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STATUS OF THE FENESTRATION OPERATION FOR OTOSCLEROSIS

Presentation of Permanently Improved Cases[1]

J. L. MAYBAUM, M.D.

Within the past few years interest of the general public and the medical profession has been aroused by the known successes obtained in otosclerosis by means of the Lempert operative procedure.

Earlier attempts at surgery for this condition had been made, the various surgical methods having as their purpose the establishment in another part of the labyrinth of a substitute window to take the place of the oval window with its fixation of the stapes.

Kessel in 1876 was the first to report an operation for otosclerosis, by removing the foot plate of the stapes. He reported that the operation was a failure. Barany in 1910 was the first to suggest a fistula in the semi-circular canal, but his operation produced improvement only for a short time. Holmgren from 1917 until 1935 made a large number of these fistulas of the labyrinth and used various substances to cover the fistula. Most of these cases eventually resulted in closure of the fistula by bone formation. Sourdille in 1924 came somewhat nearer to a solution of the problem, but his was a difficult five stage procedure. He reported his surgical technique before the New York Academy of Medicine in 1936. His report was not accompanied by accurate pre-operative and post-operative hearing tests. The audiometer had not yet been devised. It remained for Lempert to perfect a highly technical operative procedure which is done in one stage and in which a viable flap obtained from the skin over the posterior bony canal is used to cover the fenestration. He modified the original operation in important details, retaining its essential features.

In the original operation of fenestration of the horizontal canal successful results were obtained in about one-third of the cases. Later by fenestration of the vestibule, to which he gave the name, Nov-Ovalis, far better results followed. More recently, Lempert introduced the use of penicillin before and after operation, and the use of a cartilaginous stopple placed in the fenestration. These changes resulted in better healing, lessened occurrence of labyrinthitis and apparently lessened likelihood of closure of the fenestration, and gave promise of even better results (70 per cent to 85 per cent).

CLINICAL OBSERVATIONS

It is estimated that in the United States no less than 8,000,000 people are afflicted with this condition. During the progress of the hearing loss there may be periods of exacerbation, at other times the condition may remain stationary. The general condition of these patients influences the progress. Psychological factors must not be overlooked as a contributory factor to the state of hearing.

[1] Presented at the monthly general medical conference, The Mount Sinai Hospital, New York, November 23, 1945.

Pregnancy is known definitely to result in rapidly increasing loss of hearing. Many of these patients date their hearing defect to the time of pregnancy and increasing hearing loss with subsequent pregnancies.

Ear Examination. In typical cases the drums are normal or show atrophic changes through which the characteristic pinkish color of the promontory can be seen. The drums may be dull from an accompanying middle ear catarrh or scarring with or without a perforation of the drums may exist from an associated middle suppurative process. Cerumen in the ear may be absent, the patient complaining of dryness of the ear canal. In some cases ear cough reflex may be absent. Patients frequently volunteer information that they hear better in noisy surroundings, as in the subway. This symptom is called Paracussis Wilisii. An outstanding symptom and one which often gives greater annoyance than the hearing impairment is tinnitus.

Hearing test. In early cases, tuning fork and audiometer tests show pure conduction hearing impairment with normal bone conduction. Conduction by air may be much reduced. As the condition progresses there is increasing signs of secondary cochlear nerve involvement as evidenced by reduction in hearing by bone conduction, first involving the high tones, later including the middle and low-frequencies. In advanced cases audiometric tests point to marked hearing loss of the nerve type with little or no useful hearing remaining.

The Lesion. The disease process is an ankylosis of the stapes with spongification and hyperplasia of the bony labyrinthine in the region of the oval window. Later there may occur similar changes in other areas of the bony labyrinth with degenerative changes in the cochlear nerve endings. In recent years as a result of extensive histo-pathological studies, two types of cases of otosclerosis are considered: (1) *Clinical otosclerosis:* due to fixation of the stapes with typical symptoms and signs and their variations. (2) *Histologic otosclerosis:* no symptoms or signs of hearing loss but at post mortem histological studies, otosclerotic foci are found in various areas of the bony labyrinth but not involving the oval window and stapes.

Therapy. In the past all forms of therapy, endocrines, vitamins, etc. etc., have been tried with no results. Three volumes on otosclerosis issued by the American Otological Society are replete with information and in the final chapter acknowledgement is made of failure from any form of therapy.

Indication for the fenestration operation.

Clinical evidence of fixation of the stapes.

Loss of hearing by air conduction of not less than 40 decibels when accompanied with a loss of practical hearing.

Normal hearing by bone conduction determined by masking, or a loss in hearing by bone conduction, which does not exceed 30 decibels for 512-1024-2048 frequencies.

Complete absence of suppuration from the middle ear.

A completely normal and translucent tympanic membrane without perforations.

Completely intact and healthy cutaneous linings of the bony walls of the external auditory canal.

A normal state of health.

Results of fenestration operation. In the earlier operation when fenestration of the horizontal canal was being done, success was reported in about 35 per cent to 40 per cent of cases. Later the modification of Lempert's technique of making the fenestration more forward—in the vestibule of the bony labyrinth (Nov-Ovalis)—a higher percentage of permanent improvement of hearing has resulted (between 65 per cent and 75 per cent). More recently, in the past year, an even higher percentage is being reported from use of stopple (cartilaginous insert) and the use of penicillin before and after operation. Penicillin undoubtedly promotes far better healing and practically eliminates a former not uncommon complication—labyrinthitis. The latter in earlier cases before the use of penicillin, was the important reason for failure to obtain successful outcome.

Criteria for a successful result following fenestration operation. Fenestration which remains patent for over one year. Closure occurs more commonly between the third and sixth month following operation. Few if any closures are reported after a one year period. The fistula test determines question of patency of fenestration.

Audiometric tests: Immediately following fenestration there is a noticeable hearing improvement—then for a two week period or so as a result of inflammatory reaction there may be a temporary reduction in hearing followed by a gradual improvement to within the normal, practical hearing level.

Causes of failure to obtain successful results. Poorly selected case for operation. Patient must have not less than the 30 decibel level for bone conduction for conversational frequencies 500—1,000—2,000.

Inadequate training for operation, and failure to follow in minute detail the technique of Lempert. Thorough preparation over a considerable period is needed to acquire the necessary technical skill.

Post operative acute labyrinthitis.

Unexplained closure of fenestration from over-active osteogenesis; in such cases revision of fenestration and use of a stopple may overcome this tendency.

ILLUSTRATIVE CASES

The following brief case presentations illustrate many of the important points discussed in this paper. Each may be regarded as a case of otosclerosis showing permanently improved hearing following a fenestration operation performed by me two years and two months ago in two cases, and two years and eight months ago in the third case. As a result of the collective experience of eight or nine operators in a few thousand cases of otosclerosis in which the fenestration operation had been done over a period of seven years, the conclusion was reached that those cases which have a positive fistula test one year or more after operation and give evidence of improvement of hearing by air conduction to the practical hearing level, may be considered permanently improved. Closure of the fenestra takes place ordinarily between the third and sixth months post-operatively.

Case 1. M. F., aged 46, female. Five years prior to surgical intervention the patient began to notice difficulty in following her vocation of teaching because of increasing im-

pairment of hearing. Tinnitus was observed from the age of 17 years. She was aware of a paracusis and her friends would comment upon her ability to hear well in noisy places, such as the subway. She has a daughter aged 23 who apparently hears well. Pregnancy, as far as she remembers, had not increased her hearing impairment or the tinnitus. Family history as regards hearing defect is apparently negative.

The pre-operative hearing level for speech was 53 decibels. Since the Fenestration Operation the average hearing level for speech is 20 decibels, which is well within the practical hearing level. The patient has returned to her position of teaching and is now completely rehabilitated. It is now two years and 2 months since the fenestration operation was performed.

Case 2. E. F., aged 26 years, female, gave a history of gradually increasing impairment of hearing during the past five years. Tinnitus is only complained of when she is in a quiet room. Family history of hearing impairment is apparently negative.

Ear examination: The drums are normal. Tuning fork tests and audiometric examination give evidence of a conductive form of hearing impairment with high level bone conduction. The average defect for speech is 54 decibels.

I did a nov-ovalis fenestration operation two years and two months ago and since then she had maintained a hearing improvement to the practical hearing level of 20 to 25 decibels. On two occasions the hearing was much reduced and accompanied by vertigo, due to crust formation in the region of the fenestra. The vertigo disappeared, and the hearing returned to the practical hearing level immediately on removal of the crust. The patient has an active fistula symptom indicating that the fenestration has remained open.

Case 3. F. A., aged 35 years, female, gave a history of hearing impairment of 15 years duration. Tinnitus is noticed only occasionally and is much worse when she has a cold. A maternal aunt had impaired hearing beginning during adolescence. Patient has a paracusis.

Ear examination: The drums are normal. Tuning fork test and audiometric examination show a conductive mechanism lesion, bilateral, more marked in the right ear with excellent high level bone conduction. The hearing loss in the right ear is 42%, in the left ear 32%. The decibel reading for the speech frequencies is down to 50 in the right ear and 40 in the left.

A fenestration operation (Nov-Ovalis) was done by me on May 15, 1943. Since the operation the hearing improvement has been maintained to the practical hearing level of 20 and 25 decibels, and the patient has effectively resumed her duties as a secretary. Whisper before operation was heard in each ear at the distance of 4 ft., it is now heard in the operated ear at the normal distance, 20 ft.

About 8 months post-operative, following the performance of a fistula test the patient became extremely dizzy, was nauseated and vomited. These symptoms of labyrnthine involvement continued for two days, and then gradually lessened during the following four or five days. The hearing dropped from the markedly improved level of 20 or 25 decibels to the pre-operative level. After a six week interval the hearing gradually rose to the practical hearing level and has remained there to the present time—2 years and 8 months after operation. The patient undoubtedly had a traumatic serous labyrnthitis as a result of the fistula test from which she gradually recovered. It is not necessary to do this test as a routine measure as adequate information as to the hearing status can be obtained by means of audiometric examinations.

COMMENT

The three cases reported may be regarded as instances of maintained hearing improvement to the practical hearing level following the performance of a fenestration operation (Nov-Ovalis). Two of the cases were operated on two years and two months ago and one, two years and 8 months ago—well beyond the time when closure of the fenestration is likely to take place.

Neither insertion of a cartilaginous stopple or penicillin was used in any of these cases. Each of these measures had not been in use at the time of operation. Sulfadiazine was given pre- and post-operatively.

CONCLUSIONS

Hearing improvement, if maintained for one year following fenestration operation, may be regarded as permanent. This statement is based upon the collective experience of operators in a few thousand cases.

Three cases have been presented showing permanently improved hearing—two 2 years and 2 months post-operative and one 2 years and 8 months post-operative.

By means of the fenestration operation of Lempert, used in properly selected cases of otosclerosis, a successful outcome may be expected in 70 per cent to 85 per cent of the cases.

Failures result from poor selection of cases, faulty technique, over-active osteogenesis, postoperative labyrinthitis.

CONGENITAL MALFORMATIONS OF THE RECTUM AND ANUS

ERNEST E. ARNHEIM, M.D.

[*From the Pediatric Service of Dr. Murray H. Bass and the Surgical Service of Dr. Harold Neuhof, The Mount Sinai Hospital, New York*]

Congenital malformations of the rectum and anus comprise an important group of anomalies in infancy. These anomalies may involve the rectum, the anus, the urogenital organs, or combinations of these structures. Statistics of the frequency of these conditions are very variable and do not represent the proportion in the population at large. Ladd and Gross (10) reported 214 anorectal anomalies among 155,997 patients admitted to the Boston-Children's Hospital, or 1:729. Crowell and Dulin (6) reported 28 cases among 150,354 patients admitted to the University of Iowa Hospitals, or 1:5,370. Berman (3) reported 22 cases among 34,454 admissions to the Riley Hospital, Indianapolis, or 1:1,566.

EMBRYOLOGY AND PATHOGENESIS

In order to understand the pathogenesis of congenital malformations of the rectum and anus and their associated anomalies, a knowledge of the normal embryologic development of the region is necessary. Excellent discussions of the subject have been contributed by Lewis (12), Arey (1), and Ladd and Gross (9, 10).

In the 5 weeks embryo the urogenital sinus and the hind-gut empty into a common cavity called the cloaca which is separated from the exterior of the body by the cloacal membrane. By the downgrowth of a mesodermic fold, the urorectal septum, a process of separation of the urogenital tract from the rectum is normally completed by the seventh week. For a time there is a small opening between the rectum and the urogenital tract, which is known as the cloacal duct. The urorectal septum also divides the cloacal membrane into the urogenital membrane anteriorly and the anal membrane posteriorly, and these acquire external openings. A small invagination, the proctodeum, develops in the region of the future anus, and the proctodeum and the rectum join their lumens by rupture of the anal membrane during the eighth week. A bulbous enlargement of the rectum (the bulbus analis) has a position in the embryo which corresponds to that occupied by the rectal ampulla in the adult; a second swelling (the bulbus terminalis) persists for only a short period and develops into the rectal zona intermedia of the adult [Ladd and Gross (9, 10)].

The rectal and anal anomalies and their associated malformations are interpreted as arrests in development in the seventh or eighth week of fetal life. An incomplete rupture of the anal membrane results in congenital anal stenosis. A rectal stenosis arises from incomplete development of the rectum. Persistence of the anal membrane results in membranous imperforate anus. The most common malformation is that in which the rectum ends blindly at some distance

above the imperforate anus. The pathogenesis of this anomaly is not clear, but it is thought to be secondary to a deficiency in the lower posterior part of the cloaca. The anus and anal pouch may be normal and the rectum ends blindly, corresponding in the embryo to the upper end of the bulbus analis.

Fistulas between the rectum and the genito-urinary tract are established if the urorectal septum did not completely separate the rectum from the urogenital sinus, with persistence of the cloacal duct. A rectoperineal fistula forms if the anterior portion of the cloacal duct is closed and the posterior portion remains open. In the female, fistulas between the rectum and the vagina occur because as the Muellerian ducts descend, along the posterior wall of the urogenital sinus, they encounter and acquire any existing rectal fistula.

The external anal sphincter muscle develops from mesodermal components, the anus and rectum being of ectodermal and entodermal origin respectively, and is usually developed in all the types of these malformations.

CLASSIFICATION

The most useful classification of congenital malformations of the rectum and anus has been suggested by Ladd and Gross (9, 10). Four types are described as follows: Type 1, a stenosis at the anus or at a point several centimeters above the anus; type 2, an imperforate anus, the obstruction being membranous in character; type 3, (the most common) an imperforate anus, the rectal pouch ending blindly some distance above the anus; type 4, a normal anus and anal pouch, the rectal pouch ending blindly in the hollow of the sacrum.

Many infants with congenital anomalies of the rectum and anus have fistulous communications between the rectum and the genito-urinary organs or the perineum. The pathogenesis of these fistulas has been described in the embryologic review. In the male these may be rectovesical, rectourethral, or rectoperineal fistulas, whereas in the female these may be rectovesical, the more frequent rectovaginal (or recto-fossa navicularis), or rectoperineal fistulas. The frequency of these complicating fistulas is found in the following representative reports: Ladd and Gross (10), 118 fistulas in 214 cases (55 per cent); Crowell and Dulin (6), 17 fistulas in 28 cases (61 per cent); Harken (8), 7 fistulas in 25 cases (28 per cent); Berman (3), 14 fistulas in 23 cases (61 per cent); Lee (11), 10 fistulas in 16 cases (63 per cent). In the last 5 cases in the author's experience there were 2 rectovaginal fistulas, 2 rectovesical fistulas, and 1 rectoperineal fistula. The type 3 anomaly is most frequently associated with fistulas.

Other congenital anomalies may be present, most commonly cardiac, urinary, or intestinal [28 per cent of the series of Ladd and Gross (10)], and this anomaly may be the cause of death. In a previously reported case by the author (2) there was a combination of atresia of the esophagus, duodenum and rectum.

CLINICAL FEATURES

These malformations are usually noted in the newborn period because meconium has not been passed and the symptoms and signs of intestinal obstruction are present, or meconium has come through an abnormal opening such as the

penile urethra, vagina, or perineum. An adequate examination of the parts will easily make the diagnosis.

The accurate determination of the position of the blind rectal pouch has been greatly aided by the technic of roentgenologic examination suggested by Wangensteen and Rice (13). This consists of x-ray examination of the abdomen and pelvis with the child in the upside down position, and a radio-opaque object at the site of the imperforate anus. The air in the colon will rise to the top of the rectal pouch, thereby revealing its proximity to the anal canal. This method, however, may not be accurate in the first twenty-four hours of life because air may not have reached the rectum.

Roentgen examinations are also useful by the injection of radio-opaque material when there is an external fistula. In patients who have had a colostomy the distal loop may be visualized by the same method to demonstrate fistulous communications and the position of the rectal pouch.

TREATMENT

The treatment of congenital malformations of the anus and rectum will vary with the type of anomaly, and may involve a simple surgical procedure or a complex reconstructive series of operations.

Stenoses of the anus or rectum are treated by repeated dilatations of the stricture. A membranous obstruction of an imperforate anus is treated by a cruciate incision of the membrane followed by occasional dilatations. When the rectal pouch ends blindly some distance above the imperforate anus, the type of operation depends upon the position of the rectal pouch and the possibility of reaching it by a perineal approach. If the pouch is 3 cm. or more above the anal pit the surgeon may experience great difficulty in mobilizing the rectum. In addition there may be so much tension on the suture line that necrosis and a poor result are obtained; the later resultant stricture may be irreparable. Under these conditions a primary colostomy is preferable. This entails a later reconstruction of the rectum, but the end result is usually far superior to that of a primary perineal approach if the rectal pouch is high in the pelvis. In such cases, too, if the perineal approach is unsuccessful it must be followed by a colostomy with a resultant high mortality (11 deaths in 13 cases, Ladd and Gross (10)). In the perineal operation emphasis is placed on adequate freeing of the rectum so that all tension is avoided. The technic of operation is described in the case report. After the perineal operation anal dilatations are begun about the tenth postoperative day and continued daily for two or three weeks, and after that period careful insertion of the little finger can be continued by the parents until all tendency to narrowing has been overcome.

The treatment of the associated fistulas will also vary with the type of the fistula. Attempts to close rectovesical and rectourethral fistulas in infants are usually unsuccessful and should be deferred to a later age. A preliminary suprapubic cystostomy and colostomy will aid in healing. Occasionally, relief of the rectal obstruction will result in the spontaneous obliteration of such a fistula. Rectovaginal fistulas can be repaired in about half of the cases at the same time

the rectal anomaly is operated upon; much depends on the height of the fistula and the rectum. A preliminary colostomy is useful as an aid in the later repair. The technic of operation for a high rectovaginal fistula is described in the case report. Rectoperineal fistulas can be excised at the same time the imperforate anus is operated upon. Dilatation of fistulas should be rarely done and only if the child's condition is poor.

TABLE 1

AUTHOR	ABNORMALITY CURED	ABNORMALITY UNCURED	OPERATIVE MORTALITY
			per cent
Ladd and Gross (10)	116 (15)*	27 (19)	24
Crowell and Dulin (6)	9	3 (3)	25

* Numerals in parentheses represent the number of patients who died.

TABLE 2

AUTHOR	TYPE OF FISTULA	ABNORMALITY CURED	ABNORMALITY UNCURED	OPERATIVE MORTALITY
				per cent
Ladd and Gross (10)	Rectovesical	4	14 (7)	39
Lee (11)	Rectovesical	1	5 (2)	33
Crowell and Dulin (6)	Rectovesical	1	2	0
Berman (3)	Rectovesical	0	2	0
Ladd and Gross (10)	Rectourethral	2	10 (7)	58
Chandler (5)	Rectourethral	2	1	0
Lee (11)	Rectourethral	1	1 (1)	50
Berman (3)	Rectourethral	0	2 (1)	0
Crowell and Dulin (6)	Rectourethral	1	0	50
Ladd and Gross (10)	Rectovaginal	22	14 (3)	8
Crowell and Dulin (6)	Rectovaginal	0	6	0
Berman (3)	Rectovaginal	3	1	0
David (7)	Rectovaginal	2	0	0
Chandler (5)	Rectovaginal	1	0	0
Carter and Lyall (4)	Rectovaginal	1	0	0
Lee (11)	Rectovaginal	0	1 (1)	100
Ladd and Gross (10)	Rectoperineal	24	0	0
Crowell and Dulin (6)	Rectoperineal	1	2	0
Berman (3)	Rectoperineal	1	0	0

The results of treatment will vary with the type of anomaly and associated fistula, the condition of the patient, the presence of serious associated congenital anomalies, the surgical judgment and technic, and the pre and postoperative care of the patient. These factors must be evaluated in order to have a more accurate knowledge of the results. Since the type 3 anomaly is the one most frequently encountered and the one in which associated fistulas are most common, the surgical results of various authors are summarized in table 1.

Table 2 summarizes the results of treatment of fistulas associated with the type 3 anomaly.

In the experience of Ladd and Gross (10), the results of treatment of all types of malformation of the anus and rectum, there were 155 patients in whom the abnormality was cured and 18 deaths, and 40 patients in whom the abnormality was uncured and 30 deaths, an operative mortality of 25 per cent.

Harken (8) reported 25 cases of all groups with 7 patients well and 9 postoperative deaths, an operative mortality of 36 per cent.

Crowell and Dulin (6) reported 23 cases of all groups with 15 patients well or improved and 4 postoperative deaths, an operative mortality of 17 per cent.

The author's experience in 5 cases, all of type 3 associated with fistulas, is as follows: 1 rectovaginal fistula, well (perineal operation); 1 rectovaginal fistula, well [multiple operations (case report)]; 2 rectovesical fistulas, uncured (colostomies); 1 rectoperineal fistula, well. There were no deaths.

A case of type 3 anomaly and associated rectovaginal fistula is presented.

REPORT OF A CASE

History. A. S., a female infant, aged 3 weeks, was admitted to The Mount Sinai Hospital on January 6, 1943. The infant was born at term by a normal delivery. An imperforate anus was noted at birth and meconium was seen to come through the vagina. On the fourth day of life the child had convulsions, and examination revealed fever and several bullae of the skin of the upper extremities and back. After treatment with sulfadiazine for three days, the child was well except for the imperforate anus, the rectovaginal fistula, and some abdominal distension. The day before admission, the infant vomited, and attempts at feeding resulted in more vomiting on the day of admission.

Examination. The temperature was 102.4°F., and the weight 7 pounds 14 ounces. There were no abnormalities of the eyes, ears, nose or throat. The heart, lungs, and extremities were normal. The abdomen was distended; peristaltic waves were not visible. Examination of the perineum revealed a dimple in the skin at the site of the anus and a small amount of stool in the vagina.

Laboratory Data. Blood examination showed hemoglobin, 80 per cent; white blood cells, 12,700, of which there were 3 per cent segmented polymorphonuclear leucocytes, 16 per cent nonsegmented polymorphonuclear leucocytes, 64 per cent lymphocytes, 15 per cent monocytes, and 1 per cent reticulocytes. The Wassermann test gave negative results. The blood chlorides were 610 mg. per cent and carbon dioxide 51.4 vol. per cent (after hypodermoclysis of 200 cc. of Ringer's lactate solution). The urine was contaminated by stool and a culture was reported Bacillus coli and enterococcus.

A roentgenogram of the abdomen, without the use of a contrast medium fourteen hours after admission (fig. 1) revealed moderate distension of the small and large intestine; no fluid levels were present. A dense opacity filled the lower third of the abdomen and a part of the pelvis; this obscured the region of the rectum so that the lower level of the rectum could not be determined. An attempt was made to visualize the rectum by the injection of air into the vagina, but this did not leave the vagina. The location of the opacity suggested a distended bladder, although the shadow seemed too large for this organ. Accordingly, the child was catheterized and a few ounces (of urine (normal on examination) were obtained. A roentgenogram of the abdomen, without the use of a contrast medium immediately after catheterization (fig. 2) did not show the opacity. The dilated sigmoid colon was visualized in the pelvis, terminating about 5.5 cm. above the site of the imperforate anus.

The temperature was normal eight hours after admission. Although a little stool was passing through the rectovaginal fistula, this was not sufficient to relieve the intestinal obstruction as evidenced by the continuation of vomiting, the abdominal distension, and the roentgenograms of the abdomen. The high position of the rectal pouch made a colostomy the operation of necessity. An intravenous infusion of 5 per cent dextrose in isotonic

solution of sodium chloride was administered for twelve hours when operation was performed.

First Operation (January 8, 1943). With the patient under ether anesthesia, a 5 cm. oblique muscle-splitting incision in the left lower quadrant of the abdomen was made. There was an escape of clear fluid on opening the peritoneal cavity. The operative field was occupied by the distended and hypertrophied sigmoid colon. The only other organ visual-

FIG. 1. Roentgenogram of the abdomen (without the use of a contrast medium) taken on the patient's admission to the hospital, showing distension of the small and large intestine; a dense opacity is seen filling the lower third of the abdomen and a part of the pelvis; the vagina is distended with injected air.

ized was the left Fallopian tube. The anterior wall of the sigmoid colon was sutured to the parietal peritoneum with interrupted sutures of 5-0 silk, exteriorizing an area about 2 cm. in diameter. The aponeurosis of the external oblique was closed with interrupted sutures of 5-0 silk to the site of the exteriorized bowel, and a small iodoform packing was placed in the wound.

Course. The infant's condition was good at the termination of operation. The intra-

venous infusion of dextrose solution and isotonic solution of sodium chloride was given during operation and for one day after operation. A transfusion of 80 cc. of citrated blood was administered two hours after operation. Feedings of 10 per cent glucose in water were started on the first day, and an evaporated milk formula on the third day. Cough and a rise in temperature to 102°F. were noted on the third day. Examination of the chest re-

Fig. 2. Roentgenogram of the abdomen (without the use of a contrast medium) taken after catherterization of the bladder showing a disappearance of the opacity; gas outlines the rectal pouch high in the pelvis.

vealed rales in the right lung, and roentgen examination of the chest showed a pneumonic consolidation involving the upper third of the right lung. On the fourth day the temperature rose to 104°F. The pneumonia was treated by oxygen and sodium sulfadiazine for two days, at the end of which time the temperature remained normal.

During the first four postoperative days more stool was passed through the rectovaginal

fistula and there was a decrease in the abdominal distension, although the colostomy had not been opened. On the fifth day the colostomy was opened. Following this, stools came through the colostomy but also passed through the rectovaginal fistula.

A transfusion of 85 cc. of citrated blood was given on the sixth postoperative day because of a drop in the hemoglobin to 59 per cent. Following this there was a rise in the hemoglobin to 86 per cent. Roentgen examination of the chest on the eleventh day showed a resolution of the pneumonia.

Fig. 3. Roentgenologic examination of the rectal pouch with iodized oil injected into the colostomy showing the rectum terminating about 3.5 cm. above the site of the imperforate anus.

In order to determine more accurately the height of the rectal pouch, iodized oil was injected into the opening in the sigmoid on the seventeenth postoperative day. Roentgenograms in the anteroposterior (fig. 3) and lateral (fig. 4) positions revealed the dilated sigmoid and rectum terminating about 3.5 cm. above the site of the imperforate anus. The infant was discharged on the eighteenth postoperative day (aged 6 weeks), weighing 7 pounds 9 ounces.

Second Admission. The child was readmitted to the Mount Sinai Hospital on March 20, 1943, at the age of 3 months. Stools had continued to pass through the vagina as well as through the colostomy. There had been no vomiting, and the child gained 2 pounds 9 ounces in weight since the previous admission.

Examination. The abnormal features were the imperforate anus and rectovaginal fistula, the sigmoid colostomy, and an ovoid mass, about 5 cm. in diameter, in the right lower quadrant of the abdomen.

Second Operation (March 26, 1943). With the child under ether anesthesia, cutaneous incisions were made encircling the exteriorized sigmoid. The peritoneal cavity was entered. The sigmoid loop was hypertrophied and enlarged. A small, avascular area of the mesentery of the sigmoid was incised close to the bowel and a small, glass rod passed through the opening. The proximal and distal limbs of the sigmoid loop were approximated below the rod with 5-0 silk sutures and attached to the parietal peritoneum with similar sutures.

FIG. 4. Iodized oil examination of the rectal pouch in the lateral position showing the high termination of the rectum.

Small iodoform packings were placed in the wound. The original opening in the anterior wall of the sigmoid was enlarged by the excision of a small area of bowel around it. The proximal loop of the sigmoid was filled with some inspissated stool, some of which was removed; the distal loop appeared to be empty.

Course. The temperature was 102°F. on the first postoperative day and normal thereafter. The colostomy functioned well and no stool was passed through the vagina. The child was discharged on the twenty-second postoperative day.

Third Admission. The child was readmitted to the Mount Sinai Hospital on September 29, 1943, at the age of 9 months. She was well until nine days before admission when there was a prolapse of the colostomy, associated with a diminution in the number of bowel move-

ments and the passage of a little stool through the vagina. After two days stool passed through the colostomy, but the child then developed an upper respiratory infection with fever and had two convulsions on the day before admission.

Examination. The changes from previous examinations were an increase in the size and weight of the child (weight 16 pounds 15 ounces), and a firm abdominal mass below and to the right of the sigmoid colostomy. A roentgenogram of the abdomen, without the use of a contrast medium, revealed no abnormalities.

Course. On the first, third, fourth and sixth hospital days there was fever (highest temperature 102°F.). Urinalysis revealed many white blood cells, and a culture of the urine was reported to contain Bacillus coli. The temperature was normal thereafter, and the child was discharged two weeks after admission.

Fourth Admission. The child was readmitted to the Mount Sinai Hospital on November 10, 1943, at the age of 11 months. There had been occasional fecal discharge from the vagina since the last admission.

Examination. The changes from the previous examinations were an increase in the size and weight of the child (weight 17 pounds 9 ounces), a prolapse of the posterior wall of the sigmoid at the site of the colostomy, and a hard mass in the lower abdomen.

Laboratory Data. Urinalysis revealed a heavy trace of albumin, few hyaline and rare granular casts, and a moderate number of white blood cells. The hemoglobin content was 84 per cent; the white blood cell count was 14,600, with segmented polymorphonuclear leucocytes 32 per cent, nonsegmented polymorphonuclear leucocytes 10 per cent, lymphocytes 51 per cent, monocytes 4 per cent, and eosinophiles 3 per cent.

Daily irrigations of the proximal and distal limbs of the colostomy were performed.

Third Operation (November 23, 1943). With the child under ether anesthesia, the sigmoid at the site of the colostomy was dissected free from the abdominal wall, mobilizing the proximal and distal loops of the sigmoid. Crushing clamps were applied at the junction of the proximal and distal limbs, and the bowel was divided between the clamps with the knife treated with phenol. The crushing clamps were replaced by small intestinal clamps to relieve weight on the abdominal wall. Packings were placed in the wound.

Course. The child's condition was good during and after operation. An intravenous infusion of 5 per cent dextrose in isotonic solution of sodium chloride was given during operation and the first two postoperative days. The clamps were removed from the proximal and distal limbs of the colostomy on the third day. Prior to this, abdominal distension was controlled by an indwelling Levin tube and by gastric siphonage (Wangensteen). Oral feedings were started on the third day, and the colostomy functioned well.

The problem of removal of the large fecal impaction in the distal loop of the sigmoid and the rectum still remained. Repeated irrigations and oil instillations into the distal loop, and attempts at manual extraction, under ether anesthesia on one occasion, were not successful. The extension of the distal loop to the right and downward formed an angle beyond which the stool could not be expressed. The surgical plan was to expose the distal loop and to empty it by retrograde manipulation, as in the reduction of an intussusception.

Fourth Operation (December 31, 1943). With the child under ether anesthesia, a 6 cm. transverse incision dividing both lower recti muscles was made. When the peritoneum was opened the distal loop of the sigmoid and the rectosigmoid were visualized over a length of about 12 cm., from the site of the colostomy to the pelvic peritoneum. The upper one-half of the loop had a mesentery and the lower one-half was fixed against the posterior abdominal wall. The sigmoid and rectosigmoid were greatly dilated, measuring about 3.5 cm. in diameter. The bowel extended upward from the pelvis, across to the right side of the abdomen, and then formed an acute angle as it passed over to the left side to the site of the colostomy. A large hard mass of inspissated stool was palpable within the lumen of the intestine. Prolonged attempts to push the stool proximally were not successful, due to the angulation of the bowel and a narrowing proximal to the area of angulation.

A vertical incision, about 4 cm. long, was made in the anterior wall of the sigmoid. Two stony hard masses of stool were extracted through the opening in the bowel; the larger one

measured about 7.5 cm. by 3.5 cm. in diameter, and the smaller one, about 2 cm. by 1.5 cm. The wall of the sigmoid was closed transversely to its long axis with a continuous mattress suture of 5-0 chromic catgut, covered by a layer of interrupted seromuscular sutures of 5-0 silk. About 1.5 Gm. of sulfanilamide powder was scattered in the peritoneal cavity around the site of operation. The abdomen was closed with a continuous 5-0 chromic catgut suture of the peritoneum, and interrupted 5-0 silk sutures of the fascia. The subcutaneous tissues were packed with iodoform gauze, and interrupted silk sutures were passed through the skin but not tied.

Course. The postoperative course was uneventful and the temperature remained normal. The child's good condition was maintained by continuous infusion of 5 per cent dextrose in isotonic solution of sodium chloride, supplemented by plasma, during operation and the first two postoperative days. Oral feedings were started on the third day after which the colostomy functioned. The subcutaneous packing was removed and the dermal sutures were tied on the third day. The wound was healed on the sixth day when the dermal sutures were removed. The child was discharged fifty-seven days after the division of the sigmoid and nineteen days after the sigmoidotomy weighing 16 pounds.

Follow-up examination when the patient was $1\frac{1}{2}$ years of age revealed continued improvement. The weight was 17 pounds. There were three normal stools a day through the colostomy, and no fecal discharge from the vagina.

At follow-up examination when the child had reached the age of $1\frac{11}{12}$ years the normal growth and development had continued. The local condition was unchanged from the previous examination.

Fifth Admission. The child was readmitted to the Mount Sinai Hospital on January 4, 1945, at the age of 2 years, for additional operative procedures.

Examination. There were no changes from the previous follow-up examination. Mental and physical development were normal. The weight was 20 pounds 12 ounces.

Fifth Operation (January 10, 1945). With the child under ether anesthesia, in the lithotomy position, an anteroposterior incision was made in the perineum, extending from the vagina to the coccyx. The incision passed through the external anal sphincter and the perineal muscles. Dissection was continued through the ischiorectal fat pad and the levator ani muscle into the pelvis. The rectal pouch was identified in the hollow of the sacrum, about 4.5 cm. from the site of the imperforate anus. Traction sutures of 5-0 silk were placed through the tip of the pouch, and mobilization of the rectum was performed. The rectum was found to terminate in a large fistula communicating with the posterior wall of the vagina. When the fistula was excised it seemed to involve most of the posterior wall of the vagina. The defect in the posterior vaginal wall was closed with interrupted sutures of 5-0 silk. The mobilized rectum could then be brought down through the anal sphincter so that the fistulous tract was exteriorized. The perineal muscles and skin anterior, and the skin posterior, to the rectum were closed with interrupted sutures of 5-0 silk. The fistula was then excised, the rectal pouch opened, and the rectal wall sutured to the skin around the anal opening with interrupted sutures of 5-0 silk. A small rubber dam drain was left in the pelvis posterior to the anal site. The child's condition at termination of operation was good.

Course. A continuous intravenous infusion of dextrose solution and isotonic solution of sodium chloride was given during operation and for two days after operation supplemented by a transfusion of 200 cc. of citrated blood during the first postoperative day. The temperature remained normal. Oral fluids were given on the first day, milk on the second day, and a soft diet on the fourth day. The colostomy functioned on the second day. The sutures were removed on the fourteenth day and the rectal lumen appeared adequate. The perineum was examined, under anesthesia, three weeks after operation; the rectum and vagina were normal. On examination, under anesthesia, thirty-three days after operation, the anus was found to easily admit a No. 26 urethral bougie.

On the thirty-eighth postoperative day, with the child under ether anesthesia, the anus was dilated with No. 11 and 12 Hank dilators, and a spur crusher was applied to the colos-

tomy. The spur crusher was removed three days later. The anal dilatation and the application of the spur crusher, under anesthesia, were repeated on the fifty-second day; some inspissated stool was irrigated through the distal loop of the sigmoid from the rectum.

Fig. 5. Photograph of the child at the age of 3 years, showing good nutrition and operative scars.

The spur crusher was removed four days later and the spur of the colostomy was found to be destroyed. Stool passed by rectum two weeks later. Daily irrigations through the colostomy and the rectum were then started, preparatory to the closure of the colostomy, but the child resisted the insertion of the tube into the rectum, and the rectum could not be

completely emptied of inspissated stool. It was necessary to administer anesthesia on the ninety-fourth, the one hundred and fifth, the one hundred and nineteenth, the one hundred and twenty-seventh, the one hundred and fiftieth, and the one hundred and seventy-first postoperative days. On each of these occasions the anus was found to be of normal size, admitting the fifth finger. The sigmoid and the rectum were finally cleared of stool six months after the reconstruction of the rectum.

Sixth Operation (July 2, 1945). With the child under ether anesthesia, the opening in the colostomy was temporarily closed by the excision of a small segment of the surrounding skin and closure with a continuous silk suture. The proximal and distal loops of the sigmoid were dissected from the abdominal wall. The peritoneum was entered on the mesial surface. The opening in the colostomy was closed, transverse to the long axis of the bowel, with a continuous mattress suture of 3-0 chromic catgut, covered by a layer of interrupted seromuscular sutures of 5-0 silk. The sigmoid was replaced into the peritoneal cavity. The peritoneum was closed with a continuous suture of 3-0 chromic catgut, and the fascia and skin were closed with interrupted sutures of 4-0 silk.

Course. A continuous intravenous infusion of dextrose solution and isotonic solution of sodium chloride was given during the operation and for two days after operation, supplemented by a transfusion of 200 cc. of citrated blood two hours after operation. The temperature remained normal. Oral fluids were given on the first day, milk on the second day, and a soft diet on the fifth day. Sulfadiazine was administered during the first six days. Stool was passed by rectum on the fourth day. Thereafter, there were one to two normal stools a day. The wound healed by primary union and the dermal sutures were removed on the twelfth day. The child was discharged well (aged 2 years and 7 months) two years and six months after the primary colostomy, two years and four months after the glass rod colostomy, one year and eight months after the division of the sigmoid, one year and eight months after the division of the sigmoid, one year and seven months after the sigmoidotomy, six months after the reconstruction of the rectum and closure of the recto-vaginal fistula, and three weeks after the closure of the colostomy.

At follow-up examination when the child had reached the age of 2 years and 11 months, the weight was 26 pounds. The wounds were firmly healed. The anus readily admitted the fifth finger. There was usually one normal stool a day, and occasional constipation required an enema.

At the time of this report, the patient's age is 3 years, the weight 27 pounds. Mental and physical development is normal, and the patient is an alert, happy child (fig. 5).

COMMENT

This case illustrates the difficulties in management of a high rectal pouch and a fistula ending high in the vagina. Subsequent events proved that the principle of staged operations and a preliminary colostomy was a correct one. However, the number of operative procedures could have been reduced from six to three in number, and the formation of inspissated stool in the distal limb of the sigmoid could have been prevented, by a complete division of the sigmoid at the primary operation. This principle has been followed in subsequent cases.

Many surgeons have advised waiting for a reconstructive procedure in this type of case until the child is 6 to 9 years of age when the structures are larger From this limited experience I feel that there is no advantage in waiting for more than two or three years. Beyond that period the child with a colostomy becomes cognizant of the fact that he or she is not a normal individual, and one must consider the possibility of atrophy in a non-functioning anal sphincter.

SUMMARY

The embryologic, pathologic, and clinical features, and the treatment of congenital malformations of the rectum and anus are reviewed.

A case of atresia of the rectum and associated rectovaginal fistula is reported.

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LATENT SUBPHRENIC ABSCESS*

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The inherent difficulties in the early diagnosis of subphrenic abscess were recognized many years ago, as evidenced by the fact that the first clinical case on record was diagnosed on the basis of autopsy findings (Barlow, 1845), and that, not until several decades later, 1879, was the first surgical cure recorded by von Volkman. Investigation of this condition had its beginning in the anatomic studies of Martinet (1898) and Barnard (1908). Later studies by Leydon, Piquand, Elsberg, and Lockwood clarified many important facts concerning the cause, pathology, diagnosis, and clinical course of subphrenic abscess (1, 2). All the early studies reported a mortality ranging between 30 and 80 per cent. It was not until the comprehensive analysis by Ochsner and Graves in 1933 that the importance of extra-serous drainage of subphrenic abscesses was properly emphasized. Since then the increasing emphasis on early diagnosis and extra-serous drainage brought about a decided improvement in the therapy of this condition.

The great majority of subphrenic abscesses are secondary to previous intra-peritoneal suppuration. The three most common sources are suppurative appendicitis, perforated lesions of the stomach and duodenum, and diseases of the liver and biliary tract. Thus, in the large series of Ochsner and Graves, these conditions were responsible for 30.7, 29 and 12 per cent, respectively. An occasional case results from primary intrathoracic disease, blood-borne infections from distant foci (e.g. ears, tonsils, pharynx, skin), perinephritis, pelvic inflammatory disease, enteritis and diverticulitis.

The symptoms of subphrenic infection may appear in one of three characteristic ways in relation to the primary disease.

(1) The subphrenic infection may be part of a simultaneous general intra-peritoneal suppuration, as from a perforated peptic ulcer or appendix. The symptoms of subphrenic disease in these cases are usually overshadowed by those of the general peritonitis. If the patient survives the general peritonitis, the subphrenic infection may then suppurate, or subside without going on to abscess formation. At present, it is believed that only about 30 per cent of subphrenic infections become abscesses, the great majority subsiding spontaneously.

(2) Another group of subphrenic abscesses produce symptoms, often insidiously, during the convalescence of a patient who has begun to make an apparently satisfactory recovery from his primary disease. The patient again develops fever, and upper abdominal or basal pulmonary symptoms and signs may become apparent. This type of subphrenic abscess is the most common, and if constantly kept in mind, should be diagnosed early.

(3) The third type of subphrenic abscess occurs weeks or months after the initial episode. In spite of apparent recovery, there is never complete restoration of health. Weakness, lassitude, and various vague complaints persist, but

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localizing symptoms and signs are minimal or absent. The diagnosis, however, may become apparent suddenly, with the development of complications. These may take the form of: (1) thoracic complications, such as, (a) pleural effusion, (b) empyema, (c) rupture into a bronchus, (d) pneumonia, (e) mediastinal abscess, and rarely, (g) perforation into the pericardium; (2) abdominal complications, such as, (a) rupture of the abscess through the skin, (b) rupture into the general peritoneal cavity, (c) rupture into one of the viscera, as the stomach or colon.

The chronic form of subphrenic infection, however, may never produce any of these complications. It can remain localized for a long time, producing the general picture of prolonged sepsis, including cachexia. It is with this type of subphrenic abscess that we are concerned in this report.

The primary purpose of this report is to emphasize the possibility of a prolonged latent period in the development of a subphrenic abscess. Examination of the literature on the subject reveals only a few cases in which the abscess was discovered later than six months after the antecedent disease. Lockwood (2) reported two cases discovered at autopsy, one of them 18 months after a ruptured pyosalpinx, and the other 13 months after what was either a ruptured pyosalpinx or acute appendicitis. In 82 clinically diagnosed cases he found one which occurred 20 months post-operatively. Russel (4) described a subphrenic abscess developing 7 months after a perforated duodenal ulcer, and another one year after an attack of pneumonia with pleurisy and effusion. He also mentioned one case in which symptoms occurred seven years after an operation for empyema.

Rutherford (5) described a patient who developed a right loin abscess 19 months after a serious injury which caused a lacerated liver and multiple fractures. The loin abscess proved to be the superficial extension of a right subphrenic abscess.

Grove (6) reported two cases of subphrenic abscess which occurred late after the primary disease. The first was an 18 year old boy who was well for one year after operation for a perforated appendix. He then developed right upper quadrant pain, headache, malaise, anorexia, and fever. These symptoms subsided but the presence of subphrenic abscess became apparent five months later. Grove's second case was a 40 year old lawyer who also recovered from a perforated appendix. This patient remained underweight, fatigued easily and had an occasional afternoon temperature elevation for three years. He continued his law practice, however, until he suddenly developed fever, chills, anorexia, headache, and some abdominal pain. The correct diagnosis was finally made.

Gogol (7) reported a case in which, a year after removal of a perforated appendix, the sudden evacuation of foul pus through a bronchus led to the diagnosis of subphrenic abscess. Ochsner and Graves (3) reported two cases with a long latent period, one operated upon 13 months after a perforated peptic ulcer, and the other the same length of time after an abortion.

The case herewith presented had a latent period of 19 months before the subphrenic abscess was drained.

CASE REPORT

History. W. F. B., (Adm. #538963), a 50 year old German male restaurant owner, was admitted to The Mount Sinai Hospital on September 4, 1945 complaining of right upper abdominal and right flank pains, fever and chills. He had an attack of malaria in 1914, and pneumonia in 1926. Seven years ago, he began to have occasional, mild, vague "gas" pains, associated with some palpitation. These symptoms progressed until three years ago, when x-ray showed a non-functioning gall bladder. On October 5, 1943, cholecystectomy and appendectomy were performed at another hospital. Although the exact pathological report could not be obtained, it is known that the findings were those of chronic cholecystitis without stones. The common duct was not opened. A normal appendix was removed. The patient had a normal convalescence until the sixth post-operative day, when the cigarette drain was removed. He developed severe upper abdominal pain that night, and the drain was reinserted the next morning. During the following two weeks, the patient developed

Fig. 1

fever, right upper quadrant pain, and distress across the lower right chest. At that time, three weeks postoperatively, a right thoracentesis was performed and a liter of watery fluid removed. Two days later a second tap removed 300 cc. of similar fluid, but a third aspiration, three days later, showed that the effusion had disappeared. The patient felt considerably improved and was discharged from the hospital on November 5, 1943. At home, he had right upper quadrant pain, and recurrent fever, and two weeks later about 200 cc. of clear fluid was again obtained by right thoracentesis. During the ensuing 19 months, the patient had intermittent attacks of right upper quadrant pain, often extending posteriorly and into the right flank. He also complained of easy fatigability and gaseous eructation. He was able to work, however, and only occasionally consulted his physician. In April 1945, the intensity of the right upper quadrant pains increased and he noticed fever. His physician, after x-ray examination and fluoroscopy, aspirated a large amount of thick, greenish pus from the right subphrenic space. After three similar aspirations, at two day intervals, the patient felt better for a month, when the pains and temperature recurred. This time, he was treated intensively with penicillin, and on five successive days approximately 400 cc. of pus were aspirated daily with the injection of 40,000 units of penicillin into the cavity

each time. During these five days he also received a total of 480,000 units of penicillin intramuscularly. He again felt well for a month but the right upper quadrant pain, temperature and occasional chills recurred. His local physician finally decided to refer him for surgical treatment. During the weeks preceding the operation the patient was quite ill, with daily temperature elevations, right upper quadrant pain, chills, and some vomiting. He lost 17 pounds during the preceding six months, and in the month before admission, had developed mild exertional dyspnea and a slight productive cough.

Examination. On admission to the hospital on September 4, 1945, there was marked right upper quadrant tenderness, extending around to the right side. The liver was palpable three finger-breadths below the costal margin, and there was a suggestive fullness in that region. The right diaphragm was slightly elevated. Temperature, pulse, respirations, and routine blood counts and urine examinations were normal. X-ray of the chest showed an elevated right diaphragm (fig. 1). Aspiration in the seventh right interspace at the anterior axillary line yielded thick, greenish pus which cultured pure beta-hemolytic Streptococcus.

Operation. (Dr. John H. Garlock) Under local anesthesia, an oblique right subcostal incision was made and carried down beneath the fascia. The abscess was entered extraperitoneally. 1900 cc. of foul, greenish pus were evacuated. Six cigarette drains were placed down to various parts of the large cavity.

The post-operative course was uneventful. The drains were removed singly, beginning on the sixth post-operative day. At the time of discharge from the hospital, fifteen days after operation, the wound was clean, with only one rubber tube in it, and the patient felt well.

A month after discharge the patient felt well, had gained 14 pounds and the operative wound had healed.

DISCUSSION

This patient had an abscess in the right superior anterior subphrenic space for nineteen months. Although the original physician made the diagnosis, he felt that it could be adequately treated by repeated aspiration and penicillin instillation. This case is an excellent example of the futility of conservative measures for well-defined abscess cavities. It emphasizes the importance of early surgical drainage in order to insure rapid recovery. The new bacteriostatic agents will never effectively replace this simple surgical principle.

This abscess, unlike the majority, which complicate intra-peritoneal suppuration, followed a "clean" operation. The infection here must have been secondary either to the incidental appendectomy or to contamination during the cholecystectomy. The identification of the responsible organism as a hemolytic *Streptococcus* does not indicate the origin of the abscess, since 30 to 40 per cent of all subphrenic abscesses are caused by *Streptococci*. The point to be emphasized is that freedom from peritoneal infection at the time of the original laparotomy does not exclude the possibility of a subsequent subphrenic abscess.

A subphrenic abscess, as discussed above, may be relatively asymptomatic until the sudden development of one of the previously mentioned complications. Some patients show evidence of basal pulmonary disease caused by migration of the infecting organism across the diaphragm.

Subcostal tenderness on the affected side is characteristic of abscesses in the superior anterior space as in the present case, whereas tenderness along the course of the twelfth rib suggests a posterior space infection.

X-ray and fluoroscopic examinations usually show the affected leaf of the dia-

phragm to be fixed or elevated. Demonstration of gas under the diaphragm is used as a diagnostic point, but it occurs in less than half of the cases.

The operation in this case followed the fundamental principle of extra-serous drainage. Superior anterior space abscesses are best drained by the subcostal extraperitoneal approach. Superior posterior abscesses can and should be drained extrapleurally by resecting a portion of the twelfth rib and posteriorly approaching the abscess cavity.

SUMMARY

Subphrenic abscesses may have a latent, relatively asymptomatic period for many months after intra-abdominal suppuration or surgery. Careful appraisal of apparently minimal symptoms will expedite early diagnosis. A case diagnosed and operated upon nineteen months after cholecystectomy and appendectomy is herewith presented.

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ESSAYS ON BIOLOGY OF DISEASE[1]

ELI MOSCHCOWITZ, M.D.

Chapter 13

PEPTIC ULCER

The elucidation of the biology of peptic ulcer is promptly confronted with the hazard that, despite its inordinate frequency, the initial phase is not known. The difficulty arises from the circumstance that the stomach has hitherto been an inaccessible organ. Thus far the one positive clinical criterion of a peptic ulcer is the roentgen ray examination, which unfortunately is diagnostic only after the ulcer has fully matured. A patient either has a peptic ulcer or he has not; the intervening phase has been a matter of wide controversy. Moreover, the result of the roentgen ray examination is often misleading, since an ulcer may be found at operation or autopsy despite a radiographic report of normalcy; this applies even when the ulcer is not situated in an area where its demonstration by roentgen ray examination is notoriously difficult. It is altogether likely that pathologists have seen the earliest change, perhaps in the form of an erosion or a circumscribed granulomatous change in the mucosa, but positive evidence that this lesion represents the larval form of peptic ulcer is still lacking. Serial gastroscopy offers the hope that this consummation will some day be attained.

Etiology. In recent years, the view is steadily gaining ground that peptic ulcer is a psychosomatic disease. This view is based on the following observations:

1. There is a characteristic personality or constitution. Ulcer victims are intolerant, all or nothing, mentally inelastic individuals, with strong aggressive, masochistic and sadistic tendencies. They harbor grudges and do not overcome emotional strain rapidly. They are haters and fighters. From the psychoanalytic viewpoint, Alexander (1) finds that ulcer patients suppress the longing for the maintenance or revival of the infantile relation of the child to the mother, because this longing is incompatible with the dominant ambitions of the conscious personality to grow up; to be independent, masculine and active. The suppression remains as a permanent tension. Draper (2) has described various anthropomorphic characteristics of the patient with peptic ulcer, the so-called "lean hungry Cassius" type of individual; the expression is hard and tense, the eyes deep and sullen, the lines of the face are sharply drawn, the mouth is firm, the jaws sharply angled and the masseter muscles are prominent. The patients are usually cyanotic and display tendencies toward erythremia. To what extent these physical characters are phenotypic or genotypic, it is difficult to estimate. Many of the physical characters may be interpreted as results and not as fore-

[1] This is the thirteenth chapter in a series of essays by Dr. Eli Moschcowitz, in which an attempt will be made to interpret certain forms of chronic disease from the biologic viewpoint, as opposed to the current trend toward rigid classifications implying a concept of disease as a more or less static phenomenon.

According to present plans, these assays will appear in consecutive issues of the Journal of The Mount Sinai Hospital. When the publication of the projected series of essays is completed, the several installments will be assembled and printed as a monograph.—Ed.

ordained structures, so that this constitution is probably largely conditioned by factors that began after birth. In this respect, we agree with Alexander. In any event, these physical characters are absent in a considerable proportion of patients with peptic ulcer. The psychogenic characters in my experience, never are.

2. Preceding the onset of symptoms, there can nearly always be elicited the story of an emotional conflict, economic distress, the illness or death of a dear relative, the development of a powerful hate, a resentment against an adjustment to a new way of living. The latter milieu accounts unquestionably for the appalling incidence of peptic ulcer in World War II (3, 4). That the psychological insult activates an ulcer there is little question, if one may judge by the sequence of clinical events. The probability is strong by the same token that a prolonged psychological insult is an important conditioning factor in actually creating an ulcer One cannot account for the sudden onset of the typical symptoms of distress, or for a hemorrhage in one who had previously been perfectly well and had been suddenly thrust into a difficult environment. This set of circumstances has arisen time and again in this war. *Per contra*, a remission following transfer of the patient to a more secure environment, for instance a holiday, is a constant and impressive clinical observation. One may pertinently ask why peptic ulcer is not even more ubiquitous than it is in view of the psychic strain to which most of us are subject. The answer lies first, that the background or constitution is missing; and second, that it is not the psychic strain but the manner in which one meets it that is the determining factor. As White, Cobb and Jones (5) put it "It is not the objective fact of impact which is important, but the way in which it is experienced". In this interpretation a peptic ulcer is the result of the impact of a particular variety of psychic reaction upon a constitution compounded of particular psychological components. When one or the other is lacking an ulcer will not develop. The situation is quite comparable to that which obtains in pernicious anemia; the constitution in peptic ulcer may be compared to the intrinsic factor; the psychogenic insult to the extrinsic. To describe patients with peptic ulcer as "nervous and tense" is totally inadequate, and to ascribe the activating factor to "worry" is equally faulty.

3. Peptic ulcer is extremely rare in children, before the emotive and affective mental attributes develop.

4. There is testimony that peptic ulcer is rare in primitive peoples who live under little emotional conflict (6). For instance, peptic ulcer is rare among the negroes in Africa, whereas in our northern negroes it is, in our experience, almost as common as in whites. One must conclude that this is due to conflicts engendered by industrialization and competition.

It appears that peptic ulcer, like all the hyperkinetic diseases (7) is essentially a disease of civilization.

The problem now arises as to how these psychological influences are transmuted into peptic ulcer. Inasmuch as we cannot observe transitions in the human being, the answer must come through the experimental production of an ulcer.

Experimental production of peptic ulcer. Numerous attempts have been made to reproduce peptic ulcer in animals, but most have been unsuccessful except by methods that are entirely unphysiological for human beings. Moreover, such ulcers heal rapidly, do not arise in the pathway, and altogether do not resemble those in man. The most convincing results have been obtained by Mann and Williamson (8). Grossly and histologically these ulcers were identical to the human variety, in their chronicity, their morphology, both macroscopic and microscopic, and their characteristic predilection to the pathway. These ulcers were created in two ways. (a) By eliminating the duodenum and sewing the jejunum to the pylorus, and when modifications were added whereby the acid was neutralized, buffered or diluted, the incidence of peptic ulcer was 95 per cent. (b) By repeated administration of hydrochloric acid to normal dogs by continuous drip for eight hours daily, Mann and Bollman (9) created an ulcer in about 4 weeks. Daily repetitions of excess acidity depresses the neutralizing ability. Such ulcers heal in a few days after the acid is discontinued. In the type of ulcer obtained by elimination of the duodenum and its contents, an ulcer appears rapidly, in hours or less than a day. The morphology of the primary lesion represents the prototype of that which we predict will eventually be found in the human stomach. "Macroscopically, they appeared as saucer-like depressions in the mucosa about 2 cm. distal to the pylorus. In their incipience, there is always a ring of mucosa between the ulcer and the pylorus. In the earliest stages, there is a small area covered with a homogeneous gray membrane. When the membrane is sponged off, a slight depression is uncovered where the surface of the mucosa had disappeared and which bled profusely. After the mucosa is eroded, the process may proceed quickly until the wall is perforated. Microscopically, the gray membrane is composed of mucosal cell debris. In the earliest stages the injury involves only the tips of the tubules. Hemorrhages then occur between the tubules underneath the gray covering. As more of the mucosa is injured leucocytic infiltration occurs, the ulcer penetrates beneath the muscularis mucosae and the ulcer assumes the chronic type" (9). These experiments have been confirmed by Gotschlich (10) and Dragstedt (11). These experimental results prove, if nothing more, that the acid factor is vital in the production of peptic ulcer, a fact that has been clinically surmised for decades.

The acid factor in peptic ulcer. Aside from Mann and Bollman's observations, the proofs that the acid factor is a fundamental conditioning factor are the following:

1. Hydrochloric acid in excessive quantity is almost an omnipresent accompaniment of ulcer. The rare reports of achlorhydria with peptic ulcer date mostly from the period before fractional test meals and the histamine test reduced the incidence of achlorhydria appreciably and must therefore be viewed with scepticism (12).

2. Recurrence of either peptic ulcer or a gastro-jejunal ulcer following operation does not result, if complete achlorhydria is attained; this has been our experience at the Mount Sinai Hospital.

3. In the rare cases of ulceration of Meckel's diverticulum, aberrant mucosa is nearly always present, and the ulcer is found in the intestinal and not in the gastric mucosa (13, 14, 15). Indeed Matthews and Dragstedt by an ingenious operation whereby the gastric juice is diverted into the jejunum or ileum have reproduced the counterpart of a Meckel's diverticulum with aberrant gastric mucosa, and have obtained an ulcer of the jejunum in 85 per cent and in the ileum in 100 per cent of the experiments. In passing it is interesting to note that in 18 collected cases of peptic ulcer of a Meckel's diverticulum collected by Lindau and Wolff (15), all but 2 occurred in persons below the age of 15 years.

4. In over 800 cases of pernicious anemia, peptic ulcer was not found in a single instance.

5. With the Palmer test (16) in which a quantity of dilute hydrochloric acid is swallowed in suspected cases, the onset of pain is usually indicative that an ulcer is present. In most such instances, the roentgenogram shows definite changes (17).

Recently, Walpole, Varco, Code and Wangensteen (18) by repeated single daily doses of histamine (in beeswax) in cats and dogs produced erosions and all stages of ulceration including acute perforation. "These findings suggest the importance of a gradual liberation of histamine in maintaining a constant and fairly uniform stimulation of acid." Their findings are particularly significant as an explanation of the "curling ulcer" that occasionally follows extensive turns. Necholes and Olsen (19) found experimentally that after extensive burns there is a rapid and sustained increase in gastric secretion amounting to several hundred per cent.

There is every reason to believe that hypersecretion precedes the initiation of human peptic ulcer, although there is no doubt that the ulcer may continue the hypersecretion. After the ulcer has healed, hypersecretion may persist, for a time at least (Crohn, 20). There is no doubt that emotion may produce a temporary hyperchlorhydria (21, 22). Wolf and Wolff (22) demonstrated this beautifully in their laboratory assistant Tom, the victim of a large gastric fistula surgically produced after a complete closure of the esophagus which resulted after drinking hot chowder as a child. Their experiments are particularly pertinent because they illustrate the effect upon the stomach of different varieties of emotion. After an alarm reaction following fear, or after depression the mucous membrane blanched and acid secretion diminished. Following resentment or anxiety, on the other hand, the gastric mucosa was engorged and redder than normal and the gastric secretion in terms of volume and acidity was 3 times that of normal. There was also an increase in the contractions of the organ. The appearance of the mucosa was that usually reported by gastroscopists as "chronic gastritis." Furthermore, when the emotional situation was profound and prolonged, there was a corresponding increase in vascularity, secretion and mobility. These observations were confirmed by Gordon and Chernaya (23) on a patient, the victim of similar circumstances.

A highly significant observation was made by Hoelzel (24) who made daily

observations upon his gastric acidity for years. While he was passing through a period of fear owing to the anticipation of being shot, his acidity rose to appreciable heights. When he left the city so that the occasion for fear ceased, his acidity returned to normal.

Silberman (25) found that sham feeding through an esophagostomy opening in the neck caused a powerful stimulation of the peptic glands with large amounts of fluid acid and peptic titre, and in some animals a peptic ulcer formed. These observations have been confirmed by Buchner (26) and Puhl (27), although in Dragstedt's (11) hands, such an operation was without effect. The evidence is strong that a sustained hypersecretion constitutes one of the intermediary mechanisms between disturbances in the psyche and the formation of an ulcer.

In this interpretation, peptic ulcer may be regarded as a hyperkinetic disease, which means that a large part of the mechanism whereby it is created is the result of a protracted exaggeration of one of the normal bodily functions.[2]

There is little doubt that this exaggeration of normal function is mediated through the autonomic nervous system. Pavlov showed definitely that the vagus nerves are the pathways for the stimuli that created the psychic phase of secretion. There is a decrease in secretion after experimental vagotomy. Indeed, some surgeons practice this method in preparing gastric operations for peptic ulcer.

Many observers have accepted, uncritically we believe, the hemorrhagic erosion as the initial phase of peptic ulcer, because it is so frequently associated with peptic ulcer. These erosions are called acute peptic ulcer or Dieulefoy's ulcer. Some years ago we (28) reported a number of gastroduodenal erosions, in patients who had no pain and in whom the only symptom was hematemesis. We pointed out that these erosions differed from peptic ulcer in a number of ways, aside from the absence of pain. 1. These patients did not reveal the characteristic psyche of peptic ulcer. 2. The erosions are not limited to the pathway. 3. The erosions are frequently unsuspected findings at autopsy, unattended by clinical phenomena and frequently associated with other profound disorders such as shock and sepsis. 4. Such erosions can be experimentally created though with difficulty, by multiple ligation or embolization of the gastric vessels. Such erosions heal within a short time and never give rise to the callous peptic ulcer. As Mann and Bollman state bluntly "If the mucosal lesion in man which precedes the development of the characteristic peptic ulcer begins as a hemorrhage into the mucosa, it appears that many of the results of our investigation would have little if any clinical bearing" (vide supra).

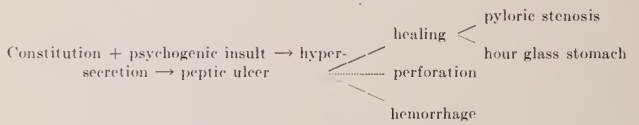
The claim that a "chronic gastritis" is the "cause" of peptic ulcer has contributed nothing to the etiology, because the "cause" of the "gastritis" is still obscure. Even assuming that a "chronic gastritis" is not secondary to the ulcer

[2] It is well to be reminded that in peptic ulcer the titre of the acid never quite attains that of the normal secretion (29). It is the increase in quantity and not the degree of acidity that is the characteristic manifestation of peptic ulcer.

and that it does not represent a normal senescent change, it does not accord with the psychological background of peptic ulcer, its distinctive localization to the pathway, the incidence of the disease in respect to sex and age, and its comparative absence in primitive races, animals and children.

After a true callous peptic ulcer has formed, its biology may proceed in various directions.

THE BIOLOGY OF PEPTIC ULCER



1. *Healing.* Superficial ulcers may heal without leaving a trace, but if the ulcer has penetrated beneath the muscularis mucosae, it is hardly likely that such an ulcer may heal without scar formation. Such scars are fairly common at necropsy examination in individuals who have previously had clinical peptic ulcers. The results of excessive scarring resulting especially in either dilatation or hour glass stomach are familiar. Clinical healing however is not always synonymous with anatomical healing. A patient may feel well with persistent niche or crater sometimes for months, after he has been "cured". The persistence of the ulcer is only one of the factors that renders peptic ulcer so subject to recurrence. Recurrence is frequent enough even after the ulcer has roentgenologically disappeared. The reason for the notorious recurrence is that one cannot divorce the human equation. Reports of "cure" of peptic ulcer by any method of therapy even after an interval of years are therefore to be viewed with reserve. In view of the basic conditioning factor of acid in the production of both peptic and jejunal ulcer, the one hope of obtaining a permanent cure is by creating a permanent achlorhydria. Thus far, only surgery in the form of subtotal gastrectomy has succeeded in this aim, but unfortunately only in a measure. It is well agreed that an achlorhydria is more likely to be attained if the ulcer is gastric rather than duodenal. In what percent a permanent achlorhydria results in both types of ulcer has not yet been determined, because the period of observation is still too short. Peptic ulcer has a long biological cycle.

2. *Hemmorrhage.* The amount varies from one that gives only the reaction for occult blood in the stool to those sufficiently large to give profound systemic reactions. These arise frequently after psychological trauma (30, 31).

3. *Perforation.* Perforation usually occurs into the general peritoneal cavity or into the lesser sac. Occasionally, if slow, it may localize in the subphrenic space. Rarely, the perforation passes into another abdominal viscus usually the colon.

4. *Carcinomatous degeneration.* The reports of the incidence of cancerous change vary widely according to the criteria employed. In some clinics it is as high as 30 per cent, and with such a high incidence, these observers advocate complete resection of all peptic ulcers as a prophylactic measure. The report of

such a high incidence is largely due to the interpretation of heterotopic proliferation of the mucosa at the edge of an ulcer as a malignant change. Using strict morphological criteria, Klein (31) subjected a series of 141 cases of peptic ulcer and 353 cases of gastric carcinoma to a careful critical review and found only two that could be considered as carcinomatous transformations of a peptic ulcer. Under any circumstances, the determination of such a change is sometimes difficult.

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MASSIVE PULMONARY EMBOLISM VII[1]

Based in Part on a Study of Eighty-eight Fatal Cases[2]

HAROLD NEUHOF, M.D., and SAMUEL H. KLEIN, Lt. Col., M.C., A.U.S.[3]

V. PROPHYLAXIS OF PULMONARY EMBOLISM

The question of prophylaxis of pulmonary embolsim has been considered from two points of view; first, that of prevention of the thrombisis from which an embolism might originate and, secondly, prevention of embolism after thrombosis has occurred. Their separate consideration is essential since certain measures advocated to prevent thrombosis (for example, measures to relieve venous stagnation and enhance venous return flow) are contraindicated after thrombosis has occurred. Each aspect will be discussed separately.

Prevention of thrombosis. As pointed out in another section, there is evidence that venous stasis and slowed blood flow are important as etiological factors in thrombosis. Thus, any plan for prophylaxis must include measures directed toward reducing these factors as much as possible. The following suggestions have been made: Abdominal dressings and binders should not be tight. Abdominal distention should be combatted vigorously whenever possible. The early administration of food is said to be helpful in stimulating peristalsis and avoiding distention. Sedation should be sufficient to relieve pain and thus permit deep breathing. Deep breathing exercises at regular intervals should be encouraged, stimulated if necessary by inhalations of carbon dioxide. The patient should be turned from side to side and as soon as possible, these movements should be carried out by the patient himself. Some authors recommend regular active exercises of the lower extremities as soon as the condition of the patient will allow. DeTakats (2) uses for this purpose a bicycle-pedal arrangement which is attached to the foot of the bed. Passive motion and centripetal massage of the extremities have been recommended if active movements cannot be performed. Based on animal experiments, Potts (97) concludes that the combination of deep breathing with active flexion of the legs is most effective in enhancing peripheral venous return. According to this author, deep breathing tends to aspirate the blood from the pelvic basin, contraction of the leg muscles squeezing the blood into the veins, and elevation of the knees making the blood run out of the femoral veins by gravity. He recommends that patients over 12 years old take 15 deep breaths morning and evening, and that they actively flex the legs with each deep breath. No clinically recognizable thrombosis or em-

[1] This is the seventh installment of a series of articles dealing with the problem of Massive Pulmonary Embolism. Upon completion of their publication they will be collected and reprinted in a single volume, constituting one of the Series of projected Monographs of The Mount Sinai Hospital Press.—Ed.

[2] From the Surgical and Medical Services and the Laboratories of The Mount Sinai Hospital, New York.

[3] Lt. Col. Klein, as adjunct surgeon to The Mount Sinai Hospital, has contributed the study of the fatal cases and the analysis on which the work is based.

bolism occurred in a series of 518 patients so treated postoperatively. Five cases of thrombophlebitis, three of which were associated with non-fatal pulmonary embolism, occurred in the control group of 95 patients with fractures which required complete immobilization. Potts concludes that while the first group comprises too small a series from which final conclusions can be drawn, the small number of cases in the control group in which embolism did occur would seem to confirm the efficacy of the prophylactic regime.

There is a difference of opinion with regard to the value of some other methods of enhancing blood flow and preventing venous stasis. Gray (96) recommends elevation of the foot of the bed approximately 10 inches for the first 24 hours after operation in order to encourage venous return from the extremities. DeTakats and Jesser (2) also place all patients after a major operation in the Trendelenburg position for 24 and occasionally 48 hours (excluding patients with intra-abdominal suppuration or with cardiac failure). A 5 per cent angle can be readily accomplished by elevating the foot of the bed for from 8 to 10 inches. Because the series in which they used this method was limited in number and in the types of cases included, they feel that the results, although suggestive, were not conclusive. In their paper, there is also illustrated, by way of contrast, the postoperative position frequently used in which the patient is semi-sitting, with the pelvis dependent and the knees bent and propped up by pillows beneath them. With the patient in this position, blood will tend to pool in the pelvis and the pressure of the pillows in the popliteal area will cause blockage of venous return from the legs. They also believe that it is especially in cases of intra-abdominal suppuration, and in thoracic or cardiac cases which require the Fowler position, that active and passive leg exercises should be performed regularly. At The Mount Sinai Hospital, it has been a rule, since 1938, on one surgical service (Service of Dr. Harold Neuhof) that virtually all adult patients must perform "pedalling" leg exercises at least twice daily under the direct supervision of the nursing staff. These bicycle exercises are performed not only by post-operative patients but also by non-operative bed patients. Although there can be no question as to a decrease in the incidence of pulmonary embolism, the problem is far from solved by this or other measures. Later reference will be made to this aspect of the subject.

Contrary to the procedure advocated by Gray (96) and deTakats and Jesser (2), Frykholm (29) recommends that the head of the bed be elevated as prophylaxis against venous thrombosis in the lower extremities. He believes that, when a patient is confined to bed, the veins of the adductor, calf and plantar muscles of the lower extremities, to a certain degree, are collapsed or pressed together so that opposing intimal lining cells come into contact. The vitality of these endothelial cells depends, to a great extent, on their contact with circulating blood. Therefore, when the veins are collapsed, the intimal cells are deprived of this source of nutrition and changes occur which initiate thrombosis. Frykholm has observed that raising the head of the bed causes the patient to slide down and press the feet against the foot of the bed, thus causing a rise in the venous pressure in the extremities so that the veins become distended with blood. In addition,

the patient tends to make active leg movements to maintain his position. In this manner, the veins tend to be rhythmically emptied and distended, thus enhancing the return of venous blood flow.

A factor that may play a rôle in the causation of thrombosis in the lower extremities and which has heretofore not been emphasized, is the practice of tightly confining the lower extremities on the operating table by means of a strap. It is conceivable that the intimal lining of the veins may thus be injured, causing thrombosis, or that the prolonged stasis produced by the strap during a long operative procedure may initiate a thrombosis.

It has been demonstrated clinically that there is an appreciable reduction in the velocity of venous return flow after operation and that, with the exception of patients suffering from thyrotoxicosis, blood flow is also retarded in non-surgical patients who are confined to bed. (Smith and Allen (37, 38), Frimman-Dahl (36.) To counteract this phenomenon, Walters (99) has suggested the use of thyroid extract, giving doses of 2 grains three times daily, beginning on the 2nd to the 4th day as soon as tolerated and continued until the patient is out of bed. In a series of 4500 cases so treated, pulmonary emboli were found at necropsy in only 4 cases. Three of these patients were more than 70 years of age and had advanced cardiac disease. In 2 cases pulmonary emboli were found unexpectedly; death was the result of uremia in 1 case. The other patient was 54 years old, had had auricular fibrillation and had died on the 6th postoperative day. She had received only 4 grains of thryoid the day before. It is noted that exercises were employed in addition to the thyroid extract in Walter's patients. Thus, the value of thyroid as a sole preventive measure is not established. Barnes (1) believes that it is desirable to use measures in addition to the administration of thyroid in order to combat the hazard of pulmonary embolism. Wright (98) suggests the routine use of heat to prevent venous stasis, which may be achieved by a heating pad covering some portion of the body. In his opinion this is more effective than the use of thyroid extract.

Bancroft and his co-workers (34) have evolved a plan of prophylaxis against thrombosis and embolism which, in addition to exercises of the extremities, the avoidance of abdominal distention, dehydration, and tight abdominal dressings, takes into consideration the tendency toward thrombosis in certain patients. They rely on a prothrombin test, made pre- and post-operatively to ascertain the "plasma clotting index." If the test shows a high fibrinogen content and plasma clotting index, the patients are placed on a carbohydrate and fluid diet, limiting their fats and proteins. These workers have shown both in dogs and in human beings that this diet, called a "bleeding diet", will diminish the bleeding factors, while a diet rich in nucleoproteins and fats will cause a marked increase in these factors. In addition, they advise the administration of sodium thiosulphate, 10 c.c. of a 10 per cent solution intravenously for three successive days, repeating the series after an interval of one day if the bleeding factors still remain high. They observed no ill effects from this therapy. In a series of 920 tested cases, 111 (12 per cent) showed high clotting indices. Only 46 per cent of these "highs"

received prophylactic treatment. In the treated group, no embolic accident occurred, while in the non-treated group there were 9 accidents.

Another method which has been suggested as a prophylactic against thrombosis is the use of heparin. There is ample experimental and clinical proof that heparin has a profound influence in preventing thrombosis which normally results from mechanical and chemical injuries to veins [Murray (100), Murray and Best (101)]. Toxic reactions have been virtually eliminated with the use of purified heparin. In a group of 315 cases treated by these authors with postoperative heparinization there were no instances of phlebitis or pulmonary embolism, though many of them had undergone the types of major surgical procedures which are believed to invite thrombosis and embolism. Hematomas occurred in 5 cases but none of these was of serious proportions and all the patients recovered. To try to obviate hemorrhage and to allow the normal processes which control bleeding, heparin is not administered for from 4 to 24 hours postoperatively. Their method is to use an intravenous drip, and to the saline solution add sufficient heparin to increase the clotting time substantially. Usually heparin is added in the proportion of 10 units of heparin to 1 c.c. of saline (1000 units or 10 mg per 100 c.c.). In the average patient this should run at the rate of about 25 to 30 drops per minute. The rate is adjusted and the effect on the clotting time is estimated every four hours. The injection is discontinued when the patient has regained normal activity, i.e., when the factors thought to contribute to the production of thrombosis have ceased to act.

Lam (102) suggests that the heparin may be administered intermittently, especially in the last few days of any course of heparin treatment, when it is advisable to have the patient get out of bed and walk without being encumbered by the intravenous apparatus. He has given the undiluted Connaught heparin in doses of 4 c.c. every three hours. Murray (103) agrees that the chief disadvantage of heparin treatment is that it is necessary for the patient to be in bed to receive the continuous intravenous injection. However, he states that in order to be effective the drug must be administered continuously because the effect of heparin is evanescent (the clotting time in a patient will return to normal within an hour after the injection is stopped). He states that intermittent injections two or three times a day are impracticable because, to make the effect of heparin last a few hours, so much must be given that the clotting time is elevated to several hours (an undesirable and hazardous treatment). Crafoord and Jorpes (104) treated 325 cases postoperatively with heparin, given as a 5 per cent sterile solution in intermittent intravenous injections four times a day. In order to obviate the possibility of hemorrhage, the heparin was not given preoperatively but was started four hours after operation. The ordinary dose was 50 + 50 + 50 + 100 (or 75 + 75 + 75 + 125) mg. daily, the treatment being continued for from five to ten days. In this series of 325 cases, there was no evidence of thrombo-embolic complications. In a control series of 1,111 similar cases thrombo-embolic complications occurred in 9 per cent. The patients selected were over 35 years of age in both series and had been submitted to operations on

the gastro-intestinal tract, the biliary system or the urinary passages, or to major operations for hernia and varices. These authors also refer to another series of 88 patients operated upon for myoma or prolapsus uteri without any thromboembolic complications. In the control series of 1054 cases there were complications in 4 per cent.

The use of dicoumarin will be referred to in the next section.

Prophylaxis for prevention of pulmonary embolism in the presence of thrombosis. Prolongation of the coagulation time of the blood with heparin has also been recommended for the prevention of pulmonary embolism in the presence of clinically manifest thrombosis or thrombophlebitis and in the treatment of the thrombophlebitis itself. Because of its expense, Priestley, Essex and Barker (105) have not used heparin routinely, but have confined its use (with a few exceptions) to two main groups of patients: 1. those in whom a non-fatal pulmonary embolus has occurred, and 2. a few patients who have had postoperative thrombophlebitis. In a preliminary report on a series of more than 55 cases treated with heparin who had had non-fatal pulmonary embolism, gratifying results were observed. They concede that heparin does not affect a thrombus which has already formed, but they feel that it does tend to prevent further increase of such a thrombus. Murray and Best (101) also state that heparin will not dissolve a blood clot or thrombus, either in vivo or in vitro. However, once thrombophlebitis has occurred, or non-fatal embolism taken place, heparinization is reported to be of great value in the alleviation of the clinical manifestations of thrombophlebitis and the prevention of recurrence of embolism. Murray (103) has described the results of treatment with heparin in more than 125 patients with thrombophlebitis, phlebothrombosis and pulmonary embolism. During the early acute phase of thrombophlebitis, pain, swelling, tenderness and fever showed improvement within a few hours and largely disappeared between 24 and 48 hours. This group of patients was treated for periods varying between 4 and 8 days at the end of which time the patients were up and about and were discharged from the hospital. There seemed to be less residual edema of the legs in these cases than in corresponding cases treated by other methods.

A group of 46 cases in which non-fatal pulmonary embolism occurred was also treated with heparin, with striking clinical improvement. While it was felt by Murray that there was no reason why further embolism should not occur in these patients, since heparin will not dissolve or remove clots or thrombi, recurrence of pulmonary embolism did not take place except possibly in two patients. The 44 other patients had no further attacks of embolism and showed rapid clinical improvement.

More recently, an anti-coagulant has been isolated which overcomes the objections of expense and continuous intravenous administration. Link and his co-workers (106) have determined the nature of, and have also synthesized the hemorrhagic principle in spoiled sweet clover disease in cattle. This substance, named "dicoumarin" (3,3′-methylenebis [4-hydroxycoumarin]) has been administered experimentally to human beings orally, as well as intravenously in the form of the sodium salt (Meyer, Bingham and Pohle (107)). The adminis-

tration in suitable doses by either route is followed (after a usually latent period of 24 hours or more) by prolongation in the prothrombin time and the coagulation time. This is sustained for several days, with a gradual return to normal levels. A safe dose has been found to be 4 to 5 mg. per kilogram intravenously or orally. The drug may also be administered orally in daily doses of 1 to 1.5 mg. per kilogram after the initial larger dose. According to these workers, dicoumarin has the advantage over heparin of potency when given orally and of relative inexpensiveness. Quick (108), however, points out three differences between the effects of the action of heparin and dicoumarin: 1. Dicoumarin requires 24 hours before it begins to inhibit coagulation, whereas heparin is active immediately after injection; 2. When the prothrombin concentration is once reduced by dicoumarin, it can be elevated only by blood transfusion. Barker (109) has reported that banked blood does not have the same effect as fresh blood in restoring the prothrombin time; 3. Dicoumarin has definitely a dilating effect on the minute blood vessels, whereas no vasodilation occurs from heparin.

Because dicoumarin when administered orally has a latent period of about 48 hours, (and even of five days, as found in one case), Evans (110) has recently used the combination of the two anti-coagulant agents, heparin and dicoumarin, to eliminate this undesirable latent period in the emergency treatment of thrombophlebitis and pulmonary embolism. He has found it safe and practicable, in 8 cases, to combine the two anti-coagulant agents according to the following plan: 1. Heparin is given intravenously immediately on making the diagnosis of phlebothrombosis, thrombophlebitis or pulmonary embolism. 2. When the clotting time is raised from twenty to twenty-five minutes, an initial dose of dicoumarin, 5 mg. per kilogram, is given orally. 3. Heparin is discontinued thirty-six hours after the initial dose of dicoumarin. 4. Dicoumarin, 1.5 to 3 mg. per kilogram, is then given daily for two to three weeks if necessary.

The administration of dicoumarin aroused an early wave of enthusiasm followed apparently by lessening enthusiasm as untoward effects such as excessively prolonged coagulation time and uncontrollable oozing of blood from wounds or other areas were noted. More recently, however, the drug is again being advocated on the basis of safer methods of administration and consistently good results are said to have been achieved. A critical survey of the literature does not as yet reveal data which can be said to establish the truth of these assertions. The data in connection with the literature on heparin are more precise and permit an evaluation of the efficacy of heparin as a prophylactic agent in venous thrombosis. A considerable literature on dicoumarin can be anticipated which may put that drug on a par with heparin. Up to the present however, heparin must be regarded as far superior as a prophylactic agent against thrombosis although its intravenous administration poses far too many problems to make possible any general use of the drug for the purpose. A painless and effective method of intramuscular or subcutaneous administration would go far towards solving the problem if it did not in fact provide a complete solution of the problem of prophylaxis of venous thrombosis.

Another method of prophylaxis against pulmonary embolism which merits

serious consideration is that of division and ligation of the femoral vein in order to prevent the migration of emboli from areas of thrombosis in the deep venous circulation of the lower extremities [Homans (111); Bauer (43); Veal (112); Sears (113); Fine and Sears (114); Starr, Frank and Fine (115); Welch and Faxon (45)]. This subject will be fully considered on the basis of personal observations and experiences but will be generally reviewed in this place. Fine and Sears were perhaps the first to offer evidence that division of the femoral vein is advisable as a *routine* prophylactic measure when thrombosis of the deep veins of the lower leg is present or suspected. As we have previously pointed out, studies reported in the literature indicate that the great majority of pulmonary emboli (excepting those of cardiac origin) arise from thrombosis of the deep veins of the lower extremities, and especially from those in the lower leg. Fine and Sears (114) feel that the cases of pulmonary embolism which may be regarded as catastrophic and for which adequate prophylactic or therapeutic measures are not available, are those of massive embolus which occur in the absence of detectable signs of venous thrombosis of the lower leg and in the absence of a previous episode of embolism. They believe that painstaking observation from the very beginning and throughout the postoperative period for the signs and symptoms of phlebitis in the deep veins of the lower leg, is likely to disclose at least suspicious evidence of thrombosis or phlebitis in a much larger number of instances than would be anticipated. This should lead to possible preventive measures in advance of the escape of an embolus. They recommend that, if the evidence of thrombosis or phlebitis in the lower leg is clear-cut, immediate division of the femoral vein below or above the profunda should be performed (bilaterally if both legs are involved). Division of the femoral vein just below the vena profunda is the most desirable site for blocking the discharge of an embolus from the deep veins of the lower leg because no proximal segment of vein with a sluggish stream is left, while the profunda and the internal saphenous remain as adequate pathways for the return flow of blood. The operative exposure necessary for this purpose permits a simultaneous examination of the vena profunda and division of this tributary if it contains a thrombus or if there is evidence of thrombosis in the deep tissues of the thigh. If division of the common femoral vein is necessary in order to shut off the profunda as well as the superficial femoral, it may be done. If embolism has not occurred, the authors consider ligation of the common femoral vein a justifiable prophylactic measure.

Welch and Faxon (45) strongly recommend that the femoral vein should be opened before it is ligated or clamped. Floating thrombi are difficult to detect by palpation through the wall of the vein, so that a tie or clamp might break off a freely floating thrombus.

Fine and Sears also state that there is no evidence that division of the femoral vein involves any significant immediate risk or adds to the disability created by the phlebitis itself. On the contrary, aside from its prophylactic value in embolism, division appears to exert a favorable influence on the course of the disease probably because of the concomitant interruption of some of the nerve pathways involved in the accompanying vasospastic reflexes. The authors admit that the

effectiveness of division of the femoral vein cannot be proved in any given case in which it is undertaken, for no one can assume that an embolus would have been discharged into the circulation. They state that its value can be affirmed with certainty only if routine division in a very large series of patients with thrombosis or phlebitis should succeed in demonstrating an incontrovertibly lowered incidence of pulmonary embolism, fatal or non-fatal. Be that as it may, the authors present 4 cases in which the protective effect of dividing the femoral vein seems to have been demonstrated. In contrast, three patients are presented in whom, in the presence of manifestations of thrombosis in the deep veins of the lower leg, a policy of further observation was pursued. These patients died of massive pulmonary embolism. In the light of available evidence, it seems logical to assume that this catastrophe might have been averted had the femoral vein been divided as soon as the manifestations of thrombosis were detected. If an embolus has been discharged, however massive it may be, so long as it is not fatal, immediate division of the femoral vein is considered to be the most effective measure remaining to prevent the discharge from its most common source of still another embolus which might prove fatal.

In cases in which the evidence of phlebitis is only presumptive, the diagnosis can be definitely determined by the venographic technique of Bauer (43) according to early authors. Differences of opinion have arisen more recently. Bauer demonstrated that thrombophlebitis may be detected in the deep veins of the lower leg even in its earliest stages. His method is described in detail by Starr, Frank and Fine (115) as follows: The patient lies on his back with the heel of the suspected extremity elevated on a six inch block. A 14 by 17 inch x-ray film (a 14 by 36 inch film with cassette is now available for filming the entire leg) is placed under the leg, its lower edge about three inches above the ankle. A small incision is made under local anaesthesia about 1 cm. behind the external malleolus. A constant small vein is found here which communicates freely with the deep system. Through a fine needle 20 c.c. of 35 per cent diodrast (Bauer uses a product called "perabrodil") is injected at a uniform rate during a period of 60 seconds. At the end of the injection the roentgen exposure is made. Resistance to the injection may be notably increased over that encountered in the absence of deep thrombosis. Another hint of the presence of thrombosis is a decidedly increased caliber of the vein at the ankle. If the foot is held in moderate inversion for the roentgenographs the shadow of the veins will not be obscured by that of the bones of the leg. The normal venogram shows the deep veins of the calf, the popliteal and the femoral vein well outlined. A few superficial veins are also seen. Thrombophlebitis is characterized by partial or complete absence of filling of the deep veins. Superficial collateral channels may be evident even in the acute stage, although they are more obvious in long-standing deep thrombophlebitis. If the venogram of an extremity is repeated, the identical pattern of normal filling or of a filling defect is obtained. On the basis of the exhaustive studies by Bauer (43) and on their own experience, Starr, Frank and Fine (115) regard a normal venogram as conclusive evidence against the existence of thrombophlebitis in the veins which are visualized.

Phlebitis has not developed at the site of injection with the diodrast, even when it is repeatedly done.[4] Diodrast has been introduced into a vein of the foot in the presence of active thrombosis without exciting any detectable reaction (Homans, 117). Nevertheless, the suggestion of Dougherty and Homans (116) has been adopted (115) that the vein be washed out with saline solution after the injection of the diodrast.

In cases in which there is phlebitis of superficial veins, and in which deep phlebitis has been excluded by venography, Welch and Faxon (45) advise ligation and division of the saphenous vein at its junction with the femoral or popliteal vein, if the patient is not in poor condition. Heat, elevation, compression bandages, incision and drainage of fluctuant areas and excision of thrombosed venous segments are also suggested as adjuvant measures.

In the presence of deep phlebitis not associated with an infarct, Welch and Faxon (45) recommend elevation, heat, sedatives and lumbar sympathetic block with procaine hydrochloride if vasospasm is considerable or pain severe, and perhaps in all cases. In patients under 40 years of age, they believe that no other treatment is required unless infarcts occur, for, on the basis of their experience, the chances of an initial fatal infarct are extremely remote. On the other hand they state that, from the ages of 50 to 70, early ligation of the femoral vein is indicated in view of an expected mortality of 7 per cent. There is an absolute indication for ligation in the age group beyond 70 years because of an expected mortality from embolus of 20 per cent. Welch and Faxon treat cases of deep phlebitis complicated by pulmonary infarction by ligation of the femoral vein, in order to prevent a 10 per cent mortality from later embolizations. These authors point out that, after a vein has been ligated, a thrombus may extend proximally until the next venous radicle is encountered. Thus, ligation of the common femoral vein may result in thrombosis extending to the bifurcation of the iliac veins. It is conceivable that this new thrombus may be the source of further emboli. Practically, however, they have never seen this happen and, on theoretical grounds, they doubt its occurrence. The theory is that thrombi are more apt to be dislodged if they are floating, one end free in the blood stream. Thus, protection from an embolus will be assured if the flow of blood is completely stopped.

In this connection, Evans (110) states that thrombosis may extend through the pelvic veins into the inferior vena cava after ligation and section of a femoral vein. For this reason he recommends that patients with phlebothrombosis be heparinized even after vein ligation and section have been performed, in order to prevent pulmonary embolism.

In cases in which pulmonary embolism has occurred in the total absence of signs and symptoms of phlebitis, venography is recommended (114, 45) in order

[4] Recently, Homans has reported an instance of severe pain and local thrombosis resulting from the introduction of a 50 per cent compound diodrast solution into the lesser saphenous vein of the leg. However, there was present in this case what might be called a thrombophilic background, and there appeared to be even a constitutional tendency in the patient and his family to thrombosis and embolism.

to demonstrate and locate the site of the thrombosis. Thus, an embolus may be assumed to have arisen from the pelvic or other inaccessible veins only when no involvement of the deep veins of either lower extremity is shown to exist in the venogram.

In view of the well-known fact that the complication of thromboembolism occurs in medical, as well as in surgical patients, the prophylactic recommendations made by Fine and Sears are applicable to all patients confined to bed, whether or not they have been subjected to an operative procedure.

CUTANEOUS MANIFESTATIONS OF SYSTEMIC DISEASE[1]

OSCAR L. LEVIN, M.D. AND HOWARD T. BEHRMAN, M.D.

There is an apparent need for the correlation of the manifestations of skin disorders with those arising in some visceral dysfunction. The association between skin diseases or cutaneous abnormalities, and internal disorders or disease patterns is not a new concept. The skin must be considered not as a covering separate from the rest of the body but as a distinctly functioning and protective cloak which has nervous, vascular and hormonal intercommunications with the visceral organs and the central nervous system. This is emphasized from time to time by many an internist and dermatologist. The former has frequently found that the detection of certain cutaneous alterations and the recognition of their character are often of considerable help in solving many a difficult problem in differential diagnosis. The dermatologist, on the other hand, has oftentimes been able to bring relief to patients in instances of obstinate skin disease by recognizing the primarily internal source of the dysfunction and thereby employing the logical therapeutic measure.

The subject matter will be presented in the form of concise descriptions of constitutional diseases exhibiting associated skin changes. Diseases of the skin of significance or diagnostic aid in the province of internal medicine will also be included. The descriptions will be listed alphabetically and briefly, avoiding lengthy dissertations and disconcerting theoretical controversies. Diseases adequately described in standard texts, such as common skin disorders and the exanthemas, are not included.

The authors acknowledge their indebtedness to numerous sources and many authorities.

ACANTHOSIS NIGRICANS

This skin disease is so frequently associated with carcinoma of the internal organs that its positive diagnosis may be considered an indication for exploratory laparotomy. The cutaneous changes are primarily brownish pigmentation of the axilla, neck, mouth, face or abdomen. In addition, small, warty or papillomatous tags are present and the normal skin markings of the involved sites are exaggerated. Approximately fifty per cent of all cases are associated with cancer, especially of the stomach (fig. 1).

ACROCYANOSIS

In this condition, the skin of the hands from the wrists to the finger tips becomes a persistent blue-red color. The palms are cold and sweaty. Acro-

[1] This is the first installment of a Synoptic Atlas of Cutaneous Manifestations of Systemic Disease. Upon completion of their publication, the installments will be collected and reprinted in a single volume, constituting one of the Series of Monographs issued by The Mount Sinai Hospital.—Ed.

cyanosis differs from Raynaud's disease in two ways. The first difference is that the skin of the fingers and hands is diffusely involved. The second point relates to the ease with which the color changes from blue to red when warmth or friction is applied to a small area, while the rest of the skin remains cyanosed. This cannot occur in Raynaud's disease because relaxation of the spasm in the proximal vessel must occur before flow can be restored through the skin of the distal

FIG. 1. Acanthosis nigricans. Triangular brownish black pigmentation on the abdomen associated with carcinoma of the lung.

parts of the finger. In acrocyanosis, it is the arterioles that are in spasm while in Raynaud's disease, the spasm involves the larger vessels.

ACRODYNIA

Pink disease or erythredema may be a juvenile variant of a deficiency of the vitamin B complex, possibly premature pellagra. In addition to the associated general changes of restlessness and irritability, the child presents an erythematous, scarlatiniform eruption of the face and body. The hands and feet are pinkish-red, pruritic and sensitive. The eruption is often associated with and followed by desquamation.

ACROMEGALY

Individuals with long standing acromegaly show alopecia, sparing the lateral and posterior margins of the scalp, and generalized hypertrichosis. In the full blown case, however, the scalp hair may be normal in addition to the striking hirsutism of the body. Women may develop heavy beards. The beard and mustache are bristly and the eyebrows bushy. The individual hairs become coarse, thick, wiry and oily. The skin is usually coarse and thickened with increased brownish pigmentation. Numerous soft fibromas of the skin are found in acromegalics. The excessive activity of the sweat and sebaceous glands leads to enlargement of the pores, seborrhea and hyperidrosis. The tongue is enlarged and prominent, the lips negroid. The nails are thickened and brittle and grow rapidly. It is characteristic of the skin in acromegaly, in contra-distinction to myxedema, that it can be lifted in folds. If the scalp itself is thrown into thick folds it is termed cutis verticis gyrata ("bull-dog scalp").

ACROSCLEROSIS

This term is limited to those cases displaying Raynaud's phenomena (intermittent arteriolar spasm of the upper extremities producing successively pallor, cyanosis and erythema) and scleroderma of the distal parts of the extremities, face and neck. The skin of the hands and fingers is smooth, shiny and tense with a pale or cyanotic color. The finger tips are frequently scarred and ulcerated with defective, abnormal nails. The fingers may be flexed and stiff. The face is ironed-out, taut and with lessened wrinkling properties. Unlike scleroderma, acrosclerosis affects women primarily and pursues a slow course. It is very important that these diseases be classified separately because of the vast difference in the prognosis, which is comparatively good in acrosclerosis. In other words, this disease does not go on to involve the entire body but remains limited to the face and extremities; it is not associated with the classic, waxy, hidebound, atrophic skin; remissions are not uncommon and the mortality is only one third of that encountered in scleroderma. Sclerodactylia is merely a less severe form of acrosclerosis.

ACTINOMYCOSIS

Primarily cutaneous actinomycosis is rare. It is usually observed secondary to infection elsewhere and its appearance on the skin follows progressive infection through the subcutaneous tissue outward to the surface. At first, it is a small nodule which gets progressively larger and ulcerative. Through the ulceration or adjoining sinus tracts, pus may be expressed. It is in this pustular discharge that the characteristic yellowish sulfur granules are found (yellowish or white flakes when spread out on a slide). The lesions may become quite large and confluent to form a nodular, board-like induration dotted with sinus tracts (figs. 2 and 3). The diagnosis is established by finding the granules in the discharge and not by cultures which may yield harmless but culturally similar saprophytes.

ADDISON'S DISEASE

The skin changes in this disease may be the first sign presented by the patient. The gradual darkening or bronzing of the skin is usually first noticed by others. The degree of pigmentation varies with the individual and the type of skin. The first changes appear on the hands and face and gradually spread over the

FIG. 2. Actinomycosis of the face. (Courtesy of Dr. Frank C. Combes)

neck, groin, scrotum, axillae and nipples. The color varies from extensive light yellow to bronzed areas, to darkly pigmented isolated spots. It is due to the presence of melanin in the epidermal cells, and is deepest over three sites:—1. parts of the body exposed to sunlight (face, hands), 2. areas subjected to pressure and irritation (belt and suspender lines, girdle areas) and 3. parts normally darker (areolae, axillae and ano-genital region). Pigmentation of the mucous membranes is characteristic and consists of small or large spots or lines of slate gray to blue-black color involving the buccal mucosa, lips, gums, conjunctiva and

vulvo-vaginal orifice. Buccal pigmentation is not specific for Addison's disease and may be seen in exopthalmic goitre, tar melanosis, arsenicalism and in certain racial groups. The changes in color are permanent, although subsequent lightening of the affected areas has been reported. This is due, in part, to the normal lessening of pigmentation in winter and its increase in summer. It is due, also, to changes in the salt and water balance with the production of a temporary hydration of the skin and an apparent lessening of the degree of pigmentation. Pruritus is uncommon, but hyperidrosis is often associated with Addison's disease. The fingernails are occasionally ridged and grooved. The hair becomes darker and has a peculiar brownish sheen.

FIG. 3. Actinomycosis of the face. (Courtesy of Dr. Howard Fox)

ADIPOSIS DOLOROSA

This disease is described under the heading of endocrine changes.

AGRANULOCYTOSIS

This disease is described under the heading of anemia (aplastic).

ALBRIGHTS SYNDROME

This syndrome is described under the heading of osteitis fibrosa cystica.

ALKAPTONURIA

This relatively uncommon error of metabolism is encountered as a recessive Mendelian characteristic in individuals unable to effect the complete catabolism of the amino acids of tyrosine and phenylalanine. Their urine accordingly contains homogentisic acid and turns black on standing. These individuals also develop ochronosis, a darkening of the skin, sclera and cartilage of the ears and nose as pointed out by J. W. Smith in an excellent review of the entire subject (figs. 4 and 5). A butterfly-shaped, brown pigmentation of the skin of the face may also be present. Less commonly, the bluish coloration of the tendons imparts a bluish color to the knuckles and the hands, and in rare instances the

FIG. 4. Pigmentation of sclera in alkaptonuric ochronosis. (Courtesy of Dr. James W. Smith.)

thenar and hypothenar eminences are pigmented brown. Several cases of exogenous ochronosis due to prolonged contact with phenol and other drugs have been reported.

AMEBIASIS

There are no characteristic skin manifestations of this disease. Rarely, ulceration of the skin due to the Endamoeba histolytica, specifically, may be associated with the chronic dysenteric type (fig. 6).

Recently many veterans returning from the South Pacific and under treatment for malaria and amebiasis have displayed skin changes of a peculiar nature. These changes should be recognized not as manifestations of the disease but as

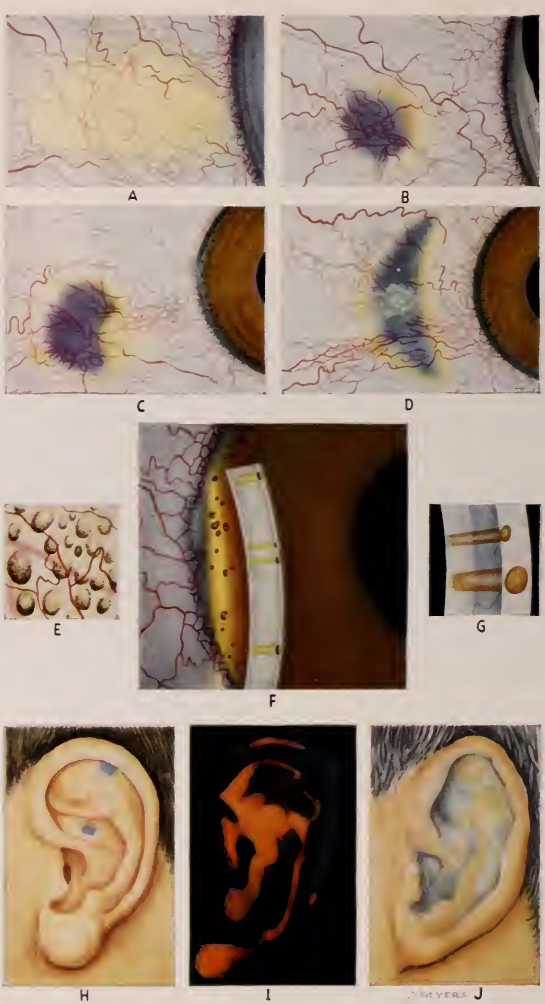

FIG. 5

reactions to its treatment with quinacrine hydrochloride. The greater number of cases present a greenish yellow coloration of the skin and a pruritic, papular and plaque-like eruption which closely resembles lichen planus. A small percentage of the patients develop an exfoliative dermatitis which is potentially serious and even fatal. It is extremely important that this syndrome be recognized by physicians because early discontinuance of the drug may prevent serious involvement and prolonged disability.

FIG. 6. Endamoeba histolytica infection of the penis. (Courtesy of Dr. Frank C. Combes and the Clay-Adams Company.)

AMYLOIDOSIS

There are three types of amyloidosis. Generalized amyloidosis, the first and ordinary type, is seen in association with diseases such as tuberculosis, syphilis and chronic suppuration. The process affects particularly the spleen, liver, kidney and adrenal glands. Infrequently, the skin may participate in this form

FIG. 5. Types of pigmentation encountered in ochronosis. (Courtesy of Dr. James W. Smith)
(a) Faint yellow-brown discoloration of right temporal conjunctiva.
(b) Scleral pigmentation in right temporal area.
(c) Gross view of right temporal scleral pigmentation showing greatest intensity in center and gradually shading into surrounding normal area. The pigment spots near the corneal limbus are seen.
(d) Advanced and extensive lesion in the left sclera and cornea. The scleral pigment is mounted toward the center.
(e) Pigmented cysts in conjunctiva at the brownish periphery of the scleral lesion depicted in C. The pigment is contained in cysts and appears to lie in the lower part, imparting the appearance of crescents or open rings.
(f) Corneal section and retroillumination. The pigment is in Bowman's zone and pushes the surface of Bowman's membrane forward. The pigment is not as dense as that in the conjunctiva. The spots project shadows which assume the brownish color of the pigment. By retroillumination the spots have the appearance of oil droplets on water.
(g) High power magnification of corneal prism shown in F.
(h) Pigment spots in left ear.
(i) Transillumination of pigment in aural cartilages.
(j) Lead blue discoloration of the left ear.

but the involvement is usually slight and not clinically apparent. The Congo red test is of value in diagnosis.

The second form of amyloidosis has been called the systematized or atypical, generalied type. In this group there is little involvement of the organs affected in generalized amyloidosis, and it is usually impossible to find a concurrent disease to account for the amyloid change. On the other hand, there is present a characteristic painful macroglossia and a copious infiltration of organs usually

Fig. 7. Amyloidosis of the skin (localized type)

spared in the generalized type (skeletal muscles, lungs, intestine and skin). By the participation of the skin in this form, there frequently appears an exanthem so characteristic, clinically and histologically, that its presence may lead to diagnosis of the internal disease. The most characteristic lesions are small, firm, shiny, glistening nodules separated by pigmented skin. They are usually grouped together over large areas of skin surface. The entire area may be so thickened, waxy and hardened that these patches resemble scleroderma and have been referred to as "pseudo-scleroderma amyloides."

The last type is the localized form of amyloidosis, and is unassociated with systemic changes (fig. 7). It appears as small groups of nodules, similar to those

already described and usually affects the extensor surface of the extremities (legs, ankles). Itching is severe (unlike the generalized types) and may precede the eruption by several years. The lesions resemble lichen planus but the translucent, single nodules, the complete resistance to therapy and the characteristic histological findings distinguish the two.

ANEMIA

The various types of anemia are associated with cutaneous changes, especially those of pallor of the skin and mucous membranes.

FIG. 8. Purpura involving the lower extremities. (Courtesy of Dr. Frank C. Combes)

A. The Normocytic anemias:

1. Hemolytic anemias are characterized by icteroid tints of the skin, and even jaundice. Purpura may be present (fig. 8). In the sickle cell variety, apparently peculiar to Negroes, pigmentation, scarring and extremely chronic ulcers of the legs are observed.
2. Aplastic anemias due to drugs are often associated with skin eruptions of the type due to chronic poisoning by the responsible chemicals (arsenic, gold, mercury). In aplastic anemias, the skin is usually strikingly pale and the sclera are bluish white. Purpura may be

present. When due to excessive exposure to roentgen rays or radioactive substance, a radiodermatitis may be associated as evidenced by pigmentation, atrophy, telangiectases, keratoses and ulceration of the skin. In those cases associated with agranulocytosis, necrotizing lesions of the throat are common. These lesions begin as discrete, edematous red patches. They rapidly coalesce to form irregularly shaped areas of gangrene, covered by a thick, tenacious, grayish white membrane and surrounded by a raised, spreading, red margin.

3. In severe chlorosis, the skin presents a yellowish green color, especially around the eyes.
4. In erythroblastosis foetalis, the skin of the infant is pale, jaundiced and edematous. In addition, petechiae and ecchymoses may be present.

   In erythroblastic anemia (Cooley's anemia), the infant or child's skin shows pallor and slight yellowing. This combination, in the usually dark-skinned racial group, causes a brownish-yellow complexion characteristic of the disease.

B. The Microcytic Anemias.

1. In patients with achlorhydria, the facial changes of rosacea (pustulation, erythema, dilated capillaries) are sometimes encountered (fig. 9).
2. The Plummer-Vinson syndrome includes patients with microcytic, hypochromic anemia, dysphagia and spoon nails. Achlorhydria may be present. The complexion is sallow, the skin dry and the hair fine. Perioral eczema and fissures at the angle of the mouth also accompany this uncommon disorder. Glossitis and kraurotic changes of the mucous membranes with eventual carcinoma formation, have been reported. The tongue may be red and sore but it is usually smooth and glazed; the papillae are atrophic. The nails are soft, friable and longitudinally striated. The dorsal concavity and upturned face margin of the nails (spoon shaped) are typical.

C. The Macrocytic Anemias.

The pallor of the skin in pernicious anemia is usually of a peculiar lemon-yellow tint. Hunter's glossitis is sometimes associated with pernicious anemia and is characterized by beefy, red varnished patches at the edge of the tongue in the early stages. Later on, the tongue shows a smooth atrophy of the papillae, especially at the margins. The hair is fine, and often prematurely gray. Vitiligo may be present.

ANKYLOSTOMIASIS

Hookworm disease produces a progressive anemia, general debility and various other symptoms. The cutaneous manifestations (ground itch) follow the entrance of larvae into the skin of the feet of persons who walk barefoot on infected ground. Itchy plaques and erythematous macules are followed by various degrees of hyperemia, vesicles, pustules and swelling. Certain members of this family, notably the Ancylostoma Braziliense (carried by dogs) produce a skin

manifestation called creeping eruption and most commonly seen in bathers along the Florida coast. The larva forms a wavy, irregular tunnel in the epidermis which may extend sinuously for several feet and cause extreme pruritus. (fig. 10).

ANTHRAX

Wool sorters disease is comparatively uncommon. The pulmonary form may be preceded by the cutaneous form or malignant pustules. The latter appears as

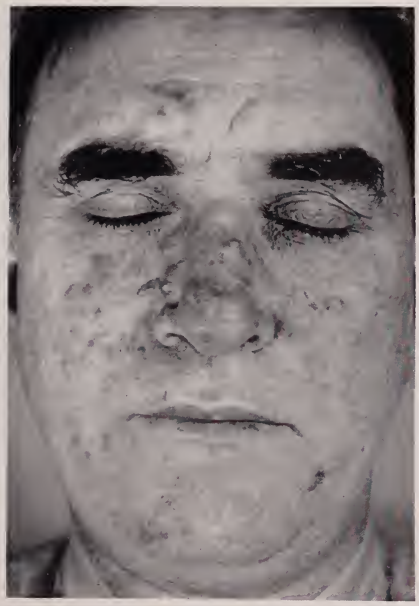

FIG. 9. Rosacea as characterized by pustules, erythema and telangiectases. (Courtesy of Dr. Frank C. Combes.)

a small, red papule following exposure to infected shaving brushes or hides. It rapidly develops numerous vesicles which rupture to form a yellow, gangrenous ulcer. By the fourth day, this erosion appears as a black crust surrounded by typical "silvery vesicles."

ARTHRITIS

In the rheumatoid form, the skin of the extremities frequently becomes smooth, glossy, atrophic and there may be marked redness of the thenar and hypothenar

eminences. The hands are usually cold and clammy. Pigmentation, resembling that encountered in Addison's disease, may lead to bronzing of the face and extremities. Vitiligo may also be present. Psoriasis occurs in approximately three per cent of the cases. This arthropathia psoriatica is seen only in association with rheumatoid arthritis and its sub-varieties, rheumatoid spondylitis and Still's disease. It assumes a severe form of chronic multiple arthritis of the rheumatoid type associated with extensive psoriatic lesions. The arthritis characteristically involves both large and small joints, especially the distal interphalangeal articulations, and parallels the cutaneous psoriatic remissions and exacerbations.

Fig. 10. Creeping eruption. The wavy, irregular tunnel in the epidermis is typical. (Courtesy of Dr. Howard Fox.)

In the hypertrophic form (osteoarthritis) the association of Heberden's nodes is common. These nodes are small, bony outgrowths of the distal side of the terminal phalanges.

In gonorrheal arthritis, the association with keratosis blenorrhagicum is not uncommon. This manifestation is described more aptly in association with gonorrhea.

In Still's disease (atrophic arthritis) annular eruptions of an erythematous nature may appear.

ASTHMA

The cutaneous manifestations observed in association with asthma are those of human hypersensitiveness in general, and are too extensive for inclusion in a

survey of this type. However, a brief classification is in order as a guide for further study. The most common skin manifestations encountered in hypersensitive individuals such as asthmatics are 1) urticaria, 2) contact dermatitis, 3) atopic eczema (neurodermatitis) and 4) the cutaneous reaction in hypersensitive states of infection (tuberculin type). The urticarias require no detailed explanation and are usually due to foods, drugs, therapeutic sera and physical agents. By contact dermatitis is meant the form of cutaneous hypersensitiveness typified by the reactions of poison ivy, furs, dyes and pollen oils, and not commonly associated with an atopic hereditary influence. Atopic eczema refers to that form of eczema which usually involves the face and extremities in children, and the flexural folds in adults. It is occasionally induced by foods, contacts or inhalants and is often associated with psycho-somatic factors. It frequently occurs in individuals whose family antecedents show an atopic influence. It may be appreciated, therefore, that the skin serves as a shock tissue in these allied states and further discussion of the phenomena of hypersensitiveness would merely lead to endless and for the purpose of this survey, pointless dissertation.

AVITAMINOSES

Vitamin A. The skin changes in deficiency states are primarily those of follicular hyperkeratosis and generalized xeroderma of the skin (fig. 11). The skin takes on an appearance of dryness, roughness and scaliness with the presence of spinous papules at the sites of the hair follicles (especially over the arms and thighs). Egg shell nails (upturned face border and translucent nail plate) may be seen in vitamin A deficiencies. The nails occasionally show transverse bands, ridging and pitting. The skin may assume a dirty, brown color and exhibit superficial ulceration. Brownish pigmentation of the conjunctiva is not uncommon. The deficiency or increased need of this vitamin may be of etiological importance in Darier's disease, ichthyosis, keratosis blenorrhagica and other dermatoses. Sjörgren's syndrome, which is concerned with the lack of vitamin A, is characterized by extreme dryness of the mucous membranes, anidrosis (due to deficient secretion of the sweat glands) and lessened secretion of the gastric juices, lacrimal and salivary glands.

Vitamin B. Thiamin chloride deficiency is not commonly associated with skin changes. Riboflavin deficiency is often associated with scaling of the lips and fissuring at the angle of the mouth. Many so-called cases of riboflavin deficiency are actually perlèche, a monilial infection which also leads to fissuring of the corners of the mouth; these cases remain unimproved with riboflavin therapy but respond to applications of gentian violet. Similarly, cases of cheilitis misdiagnosed ariboflavinosis will improve following the removal of the underlying sensitizing agent, usually lipstick. Erosions around the eyes, follicular plugging of the forehead and chin, a shark skin appearance of the nose and scaling and redness of the naso-labial folds are also classified as manifestations of riboflavin deficiency. They are not uncommonly associated, in our experience, with seborrheic dermatitis elsewhere and appear to respond well to antiseborrheal measures. However, there are certain cases presenting the above symptoms,

scrotal dermatitis and oculo-conjunctival manifestations which show definite clinical response with riboflavin therapy.

Nicotinic acid. The dermal lesions of pellagra may occur anywhere on the body. They are commonly encountered on the dorsum of the hands and feet (glove and stocking distribution), elbows, knees, ankles, neck and axillae. They are usually bilaterally symmetrical and sharply demarcated from healthy skin. At first, these areas are erythematous resembling sunburn but later on acquire

FIG. 11. Xeroderma due to avitaminosis A. (Courtesy of Dr. Howard Rapaport and Dr. Harold Herman.)

a reddish brown color and begin to scale. The underlying skin is then seen to be abnormally red and thickened. Following desquamation, the involved areas frequently become pigmented although depigmentation may also result. Successive epidosdes of pellagra may result in permanent pigmentation of the skin. In severe cases, bullous lesions (the so-called 'wet' type as distinguished from the previously described 'dry' form) may be extensive and are frequently secondarily infected (fig. 12). Photosensitization undoubtedly plays a part as manifest by the usual simultaneous involvement of the face and dorsa of the hands in individuals constantly exposed to sunlight. This factor is also of importance in

the development of the so-called pellagrous 'collarette' (dermatitis in a necklace-like distribution). The typical glossitis is characterized in the early stages by swelling and redness of the margin and tip of the tongue. Later, the entire tongue becomes smooth, swollen and fiery red.

Pyridoxine has been reported of value in acne vulgaris. We are not impressed with the results. Para-amino benzoic acid and the pantothenates have a reputed efficacy in the prevention and therapy of canities (gray hair). Outside of the development of nausea and a sickly grayish yellow color in a very small

FIG. 12. Pellagra with bullous lesions. (Courtesy of Dr. Frank C. Combes)

percentage of treated cases, no other results have been encountered by competent observers.

Vitamin C. Hyperkeratosis, as in avitaminosis A, petechiae of follicular distribution and purpura are encountered in cases of scurvy. Capillary fragility is manifest on the skin as well as in the bleeding, swollen gums and gingival petechiae. The perifollicular hemorrhage is commonest on the lower extremities.

Vitamins D and E are unassociated with skin changes.

Vitamin K deficiency and abnormal blood concentration of prothrombin may be associated with purpura.

Vitamin P deficiency is a vaguely defined syndrome and is presumably of importance in urticaria, psoriasis and other skin disease. In an extensive series of personally observed patients (with these diseases) receiving large amounts of citrin and other sources of this vitamin, we were unimpressed with the results of treatment.

AYERZA'S DISEASE

This syndrome is essentially due to an obliterative process of the smaller, pulmonary vessels sometimes on a syphilitic basis. The clinical features are intense cyanosis ("black cardiacs") dyspnea and evidence of right heart strain. The skin shows an intense and progressive cyanosis most severe about the conjunctiva, ears, lips, nose and beneath the nails.

ABSTRACTS

Authors' Abstracts of Papers Published Elsewhere by Members of the Mount Sinai Hospital Staff

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

Experimental gastric carcinoma and mucus secretion. F. Hollander. Gastro-enterol., 2: 286, April, 1944.

This is a review of the literature on the experimental induction of adeno-carcinoma in the stomachs of rodents. Although rumen and glandular stomachs are both susceptible to carcinogenesis by intra-mural injection, only the former will develop an adeno-carcinoma by topical application or ingestion. The present author ascribes this failure of carcinogenesis in the true stomach to protection by the mucus layer which lines this viscus. This interpretation can be verified by a repetition of the older experiments, modified to include the experimental breakdown of this protective mechanism, by fatigue or exhaustion of the mucous glands.

Coronary Heart Disease: Angina Pectoris, Acute Coronary Insufficiency and Coronary Occlusion. A. M. Master. Ann. Int. Med., 20: 4, 661, April, 1944.

The terms "angina pectoris" due to coronary disease, "acute coronary insufficiency" and coronary occlusion are specific and should be retained. These three types of coronary heart disease are compared from the standpoint of precipitating factors, clinical, electrocardiographic and pathological findings and pathologic physiology. Angina pectoris is a transitory attack of chest pain due to temporary myocardial ischemia, provoked by exertion, emotion, cold, etc. It is unaccompanied by organic myocardial changes. Acute coronary insufficiency refers to focal myocardial necrosis and infarction in the absence of acute coronary occlusion. It is due to prolonged myocardial ischemia and is precipitated by factors which reduce coronary blood flow or increase the work of the heart, such as effort, trauma, operation, tachycardia, heart failure, shock, etc. The E.C.G. reveals depressed S-T segments and inverted T-waves. Acute coronary occlusion occurs irrespective of external factors. It produces a confluent, through and through infarct, with the development of thrombosis and embolization and the production of a pericarditis. It is associated with deep Q-waves, elevated RS-T segments and progressive T-wave changes in the E.C.G.

Psychic Determinism in Holmes and Freud. C. P. Oberndorf. Ment. Hyg., 28: 2, 289, April, 1944.

The author points out that Oliver Wendell Holmes described many of the psychological processes with which psychiatrists have become familiar in the vocabulary of Freud and waged a fight for over fifty years against the discouraging principles of predestination and determinism in the Calvinistic sense. Holmes was convinced that the individual was no more responsible for moral obliquities and mental disorders than he was for such a natal condition as spastic paralysis. Freud whose work began about the time that Holmes had completed his career conceived behavior as determined by unconscious motivations rather than through the power of God. With this theory he pointed the way to the rectification of those deviations once thought dependent upon original sin and prenatal guilt. Determinism in all its manifestations, psychic, physical and spiritual, now became more amenable to correction. The will, to be sure, under the theories of both Holmes and Freud does not

become, cannot ever become, completely free through the force of the intellect but the work of both Holmes and Freud represents epochal psychological advances toward the understanding and cure of mental illness.

Dermatitis from Carrots. M. Peck, L. W. Spolyar and H. S. Mason. Arch. Dermat. & Syph., 49: 266, April, 1944.

Prolonged contact with raw or cooked carrots can produce allergic dermatitis. The irritant is found in the raw carrot, in the dried carrot residue, in the carrot juice, and in the heated carrot (240 F., 15 pounds' (6.8 kg.) pressure, two and one-half hours). The active principle is soluble in ether and in water. Proper precautions would reduce the incidence of dermatitis.

The Patch Test in Contact Dermatitis. L. Schwartz and S. M. Peck. Pub. Health Rep., 59: 546, April, 1944.

A detailed description is given of the technique, manifestations, evaluation and proper use of the patch test with various material. It is based on our experience with thousands of patch tests performed in the Dermatoses Section of the U. S. Public Health Service.

The Action of Atabrine on the Electro Cortico Potentials. E. P. Pick and J. Hunter. J. Pharmacol. & Exper. Therap., 80: 4, 354, April, 1944.

Atabrine in doses of 5, 10, 12 mg. per kg. given intraperitoneally or intravenously can alter the electro-corticogram of cats in nembutal anesthesia. The rapid wave frequency usually disappeared and only slow waves of low amplitude remained. This central depressant action of atabrine seems to be independent of the atabrine blood concentration and appears to be related to the atabrine content of the brain. This effect was observed within a few minutes following intravenous injection, but usually did not appear until one hour or longer after the injection; it persisted, depending upon the dose given for 1 to 4 hours. A similar atabrine action was seen in the electro-corticogram of pithed frogs following the injection of 0.5 mg. to 1 mg. atabrine. 2 mg. to 3 mg. of atabrine injected into the thoracic lymph sac blocked the righting reflexes and reduced the motility of the animals; it was followed by a reversible paresis lasting several hours or by irreversible paralysis in spite of a continued heart action, finally leading to death. Our results tend to support clinical observations of central disturbances occurring during, or following the administration of atabrine.

The Effect of Mental Activity on the Incidence of Seizures and the Electroencephalographic Pattern in Some Epileptics. H. Strauss. Psychosomatic Medicine. 6: 2, April, 1944.

The paper describes cases in which mental activity had an inhibiting influence upon epileptic attacks, particularly upon petit mal attacks. An unusual form of abnormal electroencephalogram is presented with demonstration of the influence of mental activity upon this type of electroencephalogram. The favorable effect of amphetamine sulfate upon such cases and the importance of a regulation of the activities of such patients are discussed.

Deficiency Anemia in Infants. M. H. Bass. Am. J. Dis. Child. 67: 341, May, 1944.

Nutritional anemia in its wider sense includes much more than anemia due to deficiency of iron. Severely defective formation of hemoglobin in an infant was cured rapidly by the administration of liver. It is possible that certain infants may not be able to construct the hemoglobin molecule because of a metabolic defect. A severely anemic, allergic infant being fed goat's milk recovered promptly when given a food containing protein in the form of amino acids.

The Effect of Chemotherapeutic Sulfa Drugs Upon the Growth of Hemolyticus Streptococcus W. Bierman, G. Shwartzman and S. Rosenberg. J. Lab. & Clin. Med., May, 1944.

The inherent resistance to sulfanilamide and various sulfa compounds of a strain o

α streptococcus hemolyticus isolated from a human case of subacute bacterial endocarditis remained unchanged in various media and under different temperatures.

Influence of Short Wave Current on Intraspinal Temperature. W. Bierman and S. Feitelberg. Arch. of Phys. Therapy, 25: 5, May, 1944.

With co-planar technique, the short wave current was applied to the region of the back in eleven patients. The influence of this procedure on the temperatures within the spinal canal was determined by means of thermocouples inserted through spinal tap needles before and after the application of the current. The average increase in temperature within the spinal canal was 2.6°F. In one instance the increase was 4.3°F.

Use of Tyrothricin in Treatment of Marginal Ulcers of Cornea. S. Bloomfield. Am. J. Ophth., 27: 500, May, 1944.

Tyrothricin is an antibacterial substance prepared from cultures of the bacillus brevis. The active principle in this extract is gramicidin, a polypeptide that is strongly bacteriostatic for gram positive organisma. Experiments have shown that tyrothricin may be safely instilled into the conjunctival sac in effective concentrations. This new drug may, therefore, prove valuable as a topical antiseptic in the treatment of superficial infections of the eye. Four cases of marginal ulcers of the cornea are presented, in which prolonged routine treatment with all of the more commonly used ocular antiseptics had proven ineffective. Tyrothricin was then administered as eye drops and in ointment form, in 1:5000 concentration. In each instance rapid uncomplicated healing of the lesion resulted.

Subacute Endocarditis Associated with Infection with a Spirillum. W. M. Hitzig and A. Liebesman. Arch Int. Med., 73: 5, 415, May, 1944.

The causative microorganism of an unusual case of subacute endocarditis was found to be *Spirillum minus*. The diagnosis of endocarditis was based on the classical features of low grade fever, the audible murmurs of aortic and mitral insufficiency, splenomegaly, multiple visceral and subcutaneous embolization, microscopic hematuria, petechiae, Osler and Janeway lesions and subarachnoid hemorrhage as a terminal event. The microorganism was grown in dextrose and tomato bouillon in an atmosphere of 3.5 per cent CO_2. By addition of 3–5 ml. of citrated human or rabbit blood, transplants from the original flasks were carried for 80 generations, over a period of 11 months, before they finally died out. That the microorganism isolated was identical with that of rat-bite fever, was confirmed by its cultural characteristics, its power to invade mice and its morphologic structure. The etiologic significance was clearly established by 6 repeatedly positive blood cultures during a 2-month period, and the demonstration of the organism in the crushings of the vegetations removed post-mortem. The positive serologic reactions provided additional indirect evidence that the organism causing the endocarditis was *S. minus*. Arsenicals were employed without success. Despite the unusual microorganism, the changes observed at autopsy were strikingly similar to those observed in cases of the common forms of subacute bacterial endocarditis due to *Streptococcus viridans*.

Physicians' "Storecards" and Apothecaries' Weights. Bruno Kisch. Numismatik Revue, 2: 8, May, 1944.

This is a description of coins and medals issued as advertisement for physicians, dentists and pharmacists in the 19th and 20th century and of apothecary weights in form of coins.

Anterior Chamber Irrigation with Sulfadiazine. J. Laval. Am. J. Ophth., 27: 5, May, 1944.

The description of an operation for cataract extraction is given. During the operative procedure the patient vomited and some of the vomited material got into the cul de sac of the eye which had already had the Graefe section made. After complete irrigation, 10 per cent sodium sulfadiazine in normal saline was used to flush and irrigate the anterior chamber. There was no intra-ocular irritation or inflammation following this procedure

and healing was uneventful. It is of interest to note that the anterior segment to the globe tolerates a 10 per cent solution of sulfadiazine.

Cardiovascular Injuries in the War. A. M. Master. Mil. Surgeon, 94: 5, 265, May, 1944.

Injuries of the cardiovascular system, in a broad sense, including blood vessel injuries and even inflammation, are the most important causes of violent death. When a limb is lost, death may be due to hemorrhage. Considering the fact that the chest presents a large exposed area, injuries of the heart, aorta, superior and inferior vena cava, pulmonary vessels, and also of the smaller intercostal, internal mammary, and bronchial vessels, must indeed be numerous. These wounds may be the result of bullet, bomb and shell fragments, or contusions due to air blasts or depth bom compression in the water. Arteriovenous aneurysms were treated in the classical manner by ligations, proximal and distal to the fistula, of both artery and vein, i.e., four ligations with excision of the sac. It was found that gangrene of an extremity was less apt to follow an injury to an artery if both artery and vein were ligated, since collateral circulation was encouraged when the vein was also ligated. The Naval medical officer and hospital corpsmen were only too glad to have morphine and plenty of it. The wounded, particularly those in shock, stood one-half grain doses of morphine very well, probably since the excitement and alertness of battle required counteraction. On carriers, cruisers and destroyers lost in action, there was no time for plasma because of the terrific fires and explosives. In beach landings, however, plasma was often administered within a few minutes of an injury. Blast caused petechial or capillary hemorrhages in various organs, particularly the lungs and heart. Water compression or immersion blast resulted in hemorrhages in the viscera with tarry or bloody stools, hemoptyses and hematemeses. Contusion or rupture of the cardiac wall, aorta, superior vena cava, or pulmonary vessels, occurred. Peripheral nerve palsies were often the result of hemorrhages around the nerve with resulting scar pressure.

Neurocirculatory Asthenia due to Small Heart. A. M. Master. M. Clin. North America, May, 1944.

The "small heart syndrome" is seen in asthenic persons with constitutionally small hearts who present the symptoms of effort syndrome or neurocirculatory asthenia. It is a definite problem in military life since it leads to early breakdown under the physical and mental strain of war. The most frequent complaints are fatigue on effort, rapid heart, palpitation, chest pain, shortness of breath, nervousness, fainting. This syndrome is the result of a congenital small heart. It should no longer be considered merely a nervous or functional disorder. Evidence of its "organic" nature are the lag in return of the blood pressure and pulse rate to normal following standard exercise, abnormal ECG changes in the sitting position and after exercise, diminished venous return on sitting, standing and exercise, a proclivity to fainting, diminished cardiac output and decreased oxygen saturation of the blood.

The Problem of Rheumatic Fever in the Navy. A. M. Master. Am. Heart J., 27: 5, 634, May, 1944.

In a survery of war casualties at four west coast Naval Hospitals in 1942, 80 cases of rheumatic fever were reviewed with regard to (1) the degree of disability produced by rheumatic fever in the Navy, (2) the frequency of rheumatic fever in the tropics, (3) the incidence of pre-existing rheumatic infections in childhood, and (4) recommendations concerning the acceptability for naval service of men who have had rheumatic fever. 1. Rheumatic fever is a serious epidemological problem in the Navy and causes disability. 2. Evidence is produced that rheumatic fever occurs in the tropics. 3. A history of childhood infection was obtained in 54 per cent of the cases. Other data are cited to show that rheumatic fever in adult life is probably a recrudescence of childhood disease. 4. Men who have had rheumatic fever in the past are subject to recurrence of active infection. It is recommended that such candidates be rejected for general military service.

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MYOCARDIAL INSUFFICIENCY[1]

ERNST P. BOAS, M.D.

Myocardial insufficiency is the leading cause of illness and death; it is a constant challenge to the physician in his daily rounds; yet its true nature and mechanism still elude us. When a patient succumbs to a major myocardial infarct, or to a virulent rheumatic carditis, cause and effect seem clear enough; we conclude that so much of the muscular pump has been damaged that the organ no longer can carry on the circulation. But such cases are the exception. As a rule we see heart failure supervene without manifest cause, without such overwhelming myocardial damage. When we compare at autopsy the hearts of patients who have died of myocardial insufficiency, with those of patients with similar heart lesions who have died of causes extrinsic to the circulatory system without having incurred heart failure, we are at a loss to explain the reasons for the differences in cardiac performance.

The lack of correspondence between manifest anatomical lesions of the heart, and the adequacy of the cardiac pump has long been known. Some 40 years ago Aschoff and Tawara (1) declared that there is no relationship between the gross pathological changes in the heart muscle and the functional competency of the heart. They suggested that more subtle chemical and dynamic moments, that escape detection, must play a dominant role in determining the functional adequacy of the heart.

We must seek the answer to the riddle in the fields of physiology and biochemistry. It is to Starling (2) and his followers that we owe our basic dynamic concepts of heart failure. Starling established the law of the heart, which is the same as that of skeletal muscle "that the mechanical energy set free in passing from the resting to the contracted state depends on the length of the muscle fibers." Dilatation of the heart, by giving a greater diastolic length to the heart muscle fibers enables the heart to set free more energy, to do more work. When a greater load is placed on a normal heart it temporarily dilates to meet the increased energy requirements; when a damaged heart is unable to meet the energy demands of the ordinary daily activities of the human organism, it dilates and so accomplishes the work that it did not measure up to.

The heart may be regarded as a machine that transforms chemical potential energy into work. Oxygen is a keystone of these energy transformations. The efficiency of the heart is the ratio of its external work to the energy equivalent of its oxygen consumption. Heart failure, or myocardial insufficiency occurs when there is loss of this cardiac efficiency. Starling and Visscher (3) have shown that the oxygen consumption of the heart is approximately a linear function of its diastolic volume. The amount of oxygen used by the heart depends on its degree of dilatation, more than on the work it performs. Thus a healthy heart that is

[1] This is one of the series of lectures on the Clinical Aspects of Visceral Insufficiency, read at the Blumenthal Auditorium, The Mount Sinai Hospital, New York, December 12, 1945.

not dilated will use less oxygen per minute for a given amount of work than will a dilated heart. The dilated heart is less efficient in transforming chemical energy into work. Some workers believe that heart failure is due to the lessened ability of the heart to release energy, not to an alteration of the efficiency with which the heart can convert this energy into work (4).

Within physiological limits the mechanical efficiency of the heart increases with its work. When the load on the heart exceeds the optimum, the heart continues to dilate, oxygen consumption continues to rise, but the output of work falls. Failure of the heart is characterized by a decrease in capacity for doing work at a given diastolic volume.

Since the heart is so dependent on an adequate oxygen supply, variations in coronary flow become very significant. It has been shown experimentally that when the coronary flow is diminished by adding pitressin to the coronary blood, the heart dilates. The rate of coronary flow depends on the pressure gradient between the coronary ostia in the aorta, and the coronary sinus and the Thebesian veins (5). The amount of blood drained from the coronary arteries by the coronary veins and the Thebesian veins varies. In the right ventricle approximately 90 per cent of the blood is drained off through the Thebesian system; in the left ventricle the Thebesian flow accounts for hardly 10 per cent of the blood drained from the coronary arteries, most of the coronary arterial blood escapes through the coronary sinus. Reduction of the difference in pressure between the aorta and pulmonary artery, whether caused by increased pulmonary pressure, or by diminished aortic pressure markedly reduces the flow through the Thebesian veins. This selectively impairs the nutrition of the right ventricle and causes it to dilate.

The pressure difference between the aorta and the coronary sinus determines the amount of flow out of the coronary sinus. Obstruction to the venous outflow from the coronary sinus impedes the coronary circulation. It may be said to cause a passive congestion of the heart muscle. With the onset of heart failure the venous pressure becomes elevated. This increased pressure within the right auricle and right ventricle initiates a vicious cycle—it lessens the coronary flow and this in turn increases the failure of the heart muscle, so leading to a still greater elevation of the venous pressure. The oxygen supply cannot keep up with the increasing needs of the failing heart. A low aortic pressure also will decrease the coronary flow and impair the nutrition of the heart.

Because of the difference in coronary venous outflow in the two ventricles, they behave differently under stress. Conditions leading to high left ventricular pressure do not affect the coronary flow, but those causing high right ventricular pressure do. That is why the left ventricle can beat for years without failing against heavy loads, such as those induced by hypertension or aortic valvular disease, whereas the right ventricle working against great loads fails more rapidly, and rarely recovers adequately.

Thus we have learned to regard cardiac dilatation as an advantageous adaptation of the heart to increased burdens. It is only when such dilatation exceeds certain limits that it leads to heart failure. When the overload of the heart is long continued, whether as a result of physiological stresses such as those sus-

tained by certain athletes, or as a result of disease, cardiac hypertrophy occurs. The mechanism of its development is unknown, but it seems probable that it is always preceded by dilatation. Hypertrophy enables the heart to contract more vigorously and efficiently under increased loads without having to undergo further dilatation; the hypertrophied muscle is able to perform a given work with a shorter initial length. With each new overload, however, further dilatation, followed by greater hypertrophy may ensue. As this progresses it may lead to serious disadvantages.

The nutrition of the heart muscle fibers depends on the capillary blood flow. In the hypertrophied heart the number of capillaries is not increased, and as the muscle fibers increase in diameter, the capillaries are pushed farther apart. Thus the concentration of capillaries per unit area of muscle decreases in proportion to the degree of hypertrophy. It has been estimated that the capillary surface available to diffusion in a cubic centimeter of normal heart muscle is 1200 square centimeters, in the hypertrophied muscle only 625 (6). Furthermore, the distance from the capillary wall to the muscle mass which it supplies becomes greater in the hypertrophied heart. It seems likely that these altered anatomic arrangements of the capillaries in hypertrophied hearts may contribute to a disturbed nutrition of the heart muscle, and so to its failure (7). It may be pertinent to recall that failing hearts, with rare exceptions, are hypertrophied hearts.

The preceding discussion reveals that we have arrived at some understanding of the dynamics of the circulation and of heart failure. But beyond these physical phenomena, that can be measured, lie the hidden chemical processes that enable the heart muscle to transform its latent chemical energy into mechanical energy. We are but at the threshhold of understanding these complex processes. We know that cardiac activity depends on an adequate supply of oxygen and sufficient reserves of glycogen and of phosphocreatine; that the heart is more sensitive to oxygen lack than is skeletal muscle, and that with anoxemia it tends to lose glycogen rapidly and accumulate lactic acid. Several observers have found a relationship between the creatine content of heart muscle and its function. Cowan suggested that the cardiac reserve parallels its creatine content. Bodansky found on the average a lower creatine content in the muscle of failing hearts than of normal ones (8). The results are not constant, but he suggests that an increased load on either ventricle tends to lower the creatine content of its muscle mass. Harrison has suggested that loss of potassium from heart muscle may be a factor in producing cardiac fatigue. Some support for this view comes from observations in patients with periodic paralysis. In them an episode of paralysis is associated with a drop in serum potassium from a normal of 4.7 milliequivalents per liter to 3.8 or even 1.2. A relative decrease in potassium seems to be as important as the absolute potassium level. In such patients a period of paralysis may be associated with cardiac dilatation, the development of an apical systolic murmur, and accentuation of the pulmonic second sound, weak heart sounds and electrocardiographic changes (9). These alterations in cardiac function can be promptly abolished by the administration of potassium salts.

Thiamin chloride is closely concerned with the oxidative processes in heart

muscle, with impairment of the enzyme and coenzyme systems, and lack of vitamin B_1 may lead to severe, even fatal heart failure, as in beriberi. Here, too, we are ignorant of the intimate chemical processes that take place. In the United States the full clinical picture of the beriberi heart is seen only in alcoholics with evidences of serious vitamin B_1 deficiency. Such patients may complain of dyspnea, palpitation, precordial pain and may even exhibit caridac enlargement, right and left ventricular failure, tachycardia, gallop rhythm, edema, changes in the electrocardiogram such as depression of the ST segments, inversion of the T waves, prolongation of electrical systole (10). The systolic blood pressure may be elevated and in spite of the heart failure the circulation time may be rapid, probably because of the peripheral vasodilation. Fever, exercise or hyperthyroidism, which increase the requirement for vitamin B_1 may precipitate such cardiac failure. The chemical disturbances can lead to structural changes such as hydropic degeneration of the myocardial fibers, swollen collagen and perivascular edema. Although the fully developed syndrome is uncommon in this country, there must be many borderline cases in which a low availability of vitamin B_1 contributes to the chemical changes leading to heart failure.

Alterations in balance of the several glands of internal secretion may contribute to heart failure by disturbing the chemical processes of the myocardium. I need but refer to the situation in hyperthyroidism, in hypothyroidism, in adrenal insufficiency, and following overdosage with desoxycorticosterone.

Changes in the composition of the blood, apart from its oxygen content may affect the chemical processes in the heart muscle, and alter its metabolism. The most evident of such defects is anemia. This operates by diminishing the oxygen carrying power of the blood. The minute volume flow is increased to compensate for the lessened oxygen content of each unit of blood, and at the same time the overburdened myocardium, like the other body tissues, does not obtain an adequate oxygen supply. If the hemoglobin remains under 50 per cent for months, dilatation and hypertrophy will develop in a normal heart. This is a compensatory adjustment for myocardial weakness induced by prolonged anoxemia. In the days before liver therapy, patients in the late stages of pernicious anemia often exhibited cardiac enlargement, and myocardial insufficiency. Today this syndrome is less common; it occurs in sickle cell anemia, and in the anemia that accompanies multiple hereditary telangiectases.

In a heart that is already damaged, anemias of lesser degree and duration may contribute to heart failure. Thus older persons with secondary anemia due to hemorrhoidal or uterine bleeding, or to hemorrhage from a peptic ulcer may develop heart failure. Nutritional anemia, which is so common in patients with chronic cardiovascular disease, often contributes to myocardial weakness and impedes recovery of cardiac function.

It is common knowledge that a low serum protein level contributes to the formation of edema. This is more significant in the presence of heart failure, for with elevation of venous pressure the critical level at which a lowering of blood protein will induce edema is higher than when the lowered colloid osmotic pressure of the blood is the only factor. In patients with chronic heart disease mal-

nutrition is the chief factor that brings about a lowering of serum protein; loss of albumin in the urine, and in the fluids withdrawn by paracentesis of the chest and peritoneum may be a contributing element. Another cause for the lesser percentage of protein in the blood in cardiac failure is the dilution of the blood plasma that results from the increased blood volume.

Thus chemical changes in the internal and external environment of the heart muscle; alterations in oxygen content, in available vitamins or hormones, in iron, protein and in certain salts play a significant role in the genesis of myocardial insufficiency.

The cardiac output in patients with heart failure is diminished relative to the body's metabolic requirements. The reduction in the output per beat is greater than that of the output per minute because of the increase in the heart rate. The heart may cope with an added load by increasing its rate of contraction. In this manner the minute volume flow can be increased without augmenting the stroke volume. But the energy cost is increased, the shortened diastole gives less time for the recovery process between contractions, and may impair such recovery. Tachycardia is an inefficient method of compensating for increased loads, and may in time contribute to myocardial failure. A paroxysmal tachycardia lasting several days may induce failure in a heart that is otherwise healthy, and commonly precipitates failure in a damaged heart. There are certain instances in which an increase in heart rate represents the only method of increasing the minute volume flow. Such are cases of stenosis of the aortic or mitral valves. The narrowed valvular orifice prevents the outflow of an augmented or even of a normal volume of blood per beat, so that the minute volume flow can be maintained only by an accelerated heart rate. Slowing the heart rate below the critical level in such patients may induce heart failure or anginal pain. I have observed patients with aortic stenosis who were without symptoms at heart rates of about 90, but who developed anginal pain or dyspnea when, as a result of intermittent partial heart block, the heart rate dropped to 50 or 60. A woman with a tight mitral stenosis developed a sino-auricular block with a heart rate of 40. She became quite dyspneic and developed evidence of congestive failure. When the heart rate was restored to 80 these signs and symptoms disappeared.

When the heart fails, a host of changes occur in other organs and tissues and these in turn lead to further embarrassment of the heart. This is not the place to consider them in detail. It will suffice to enumerate a few of the most important ones.

When the heart becomes insufficient there develops pulmonary congestion with engorgement of the pulmonary vessels. Because of the increased volume of blood in the lungs they contain less air than normal, they become more rigid, or less elastic, and the dead air space is increased. Pulmonary ventilation and the exchange of gases between the alveoli and the pulmonary capillaries is interfered with and this contributes to anoxemia and to further impairment of myocardial function. Reflexes arising in the congested lungs are in large measure responsible for the development of dyspnea.

Edema is the result of myocardial insufficiency, but once developed places a

greater burden on the heart. Edema formation is induced by a variety of factors, one of the important ones being the elevation of venous and capillary pressures. Yet the appearance of edema is not directly correlated with the height of the venous pressure (11). Contributing to its genesis are anoxemia, a lowering of the plasma protein, the absence of normal lymphatic flow (12), the lowered tissue tension induced by malnutrition and prolonged bed rest, and the sodium chloride balance.

The development of effusions in the serous cavities act as a further mechanical embarrassment to the failing heart. It has always been a matter of interest to understand why a right pleural effusion is more common than one on the left side, and why some patients develop ascites rather than pleural transudates. Baccelli (13) was probably the first to suggest that in patients with mitral stenosis, pressure of the dilated auricles on the major azygos vein favored the development of right pleural effusions. This theory was substantiated by Stengel in later anatomical studies (14). Ascites is particularly common in tricuspid insufficiency. Elias and Feller (15) as a result of careful anatomical studies claim that with tricuspid insufficiency, the tubercle of Lower in the right auricle between the superior and inferior vena cava becomes enlarged, and deflects the blood stream causing a selective dilatation of the lower part of the right auricle, and greater pressure on the hepatic veins, which become unusually dilated. They also point out that one reason for early hepatic enlargement, preceding edema of the legs in heart failure, is the paucity of anastomoses in the hepatic and portal venous systems, in contrast to the rich anastomoses in the domain of the inferior vena cava.

Changes in the blood volume and in the fluid balance of the body always accompany heart failure. They result from the many physiological disorders that we have just discussed and in turn place an added burden on the heart. Very often these secondary changes serve to perpetuate heart failure, in spite of the institution of therapeutic measures to restore myocardial function. A clear understanding of the mechanism of this disturbed fluid balance underlies intelligent and successful treatment.

As a result of slowing of the blood stream, diminished cardiac output, and increased venous pressure the kidneys excrete less water and salt. Oliguria is an early sign of myocardial weakness. Added to the factors that were discussed in connection with the genesis of edema, it leads to retention of salt and fluid in the body, and to increase in blood volume. This increased volume of blood is very evident at autopsy of a patient who has died in heart failure—all of the blood vessels are engorged with blood that actually drips from all of the organs. Studies in blood volume in the living have shown that the rise in blood volume parallels the increase in venous pressure and the slowing of the circulation time (16). Both the volume of plasma and the number of red blood cells increase progressively with advancing heart failure. During recovery the plasma volume diminishes first, and this is followed by a drop in the number of red blood cells. These changes may take place within a few days.

The increased blood volume increases the work of the heart, and the greater

water content of the organs and tissues further impedes the blood flow, and interferes with the respiratory exchange. The dramatic success achieved by therapy with mercurial diuretics rests on the fact that they promptly rid the body of its excess water and salt and lead to a reduction in blood volume. In appropriate cases phlebotomy, or the application of tourniquets to the extremities relieve the laboring heart by reducing the circulating blood volume.

Doctors have learned to employ diuretics in the presence of peripheral edema or anasarca, but all too often they forget that long before these gross manifestations appear, the heart is already struggling against an increased blood volume. While the accurate measurement of blood volume is not adapted to clinical use it is very simple to recognize fluid retention by observing the weight of the patient. Close to ten pounds of invisible edema may accumulate before outward signs of it become manifest. At this latter stage the blood volume will already be increased, and an unnecessary burden placed on the failing heart. It is essential, therefore, to recognize such fluid retention at its very onset.

One still hears doctors remark that a patient does not need digitalis or diuretics because there are no rales in the lungs, no swelling of the liver and no edema. These are the late manifestations of heart failure, which we can often prevent. Storage of blood and fluid in the lungs due to left heart failure leads to dyspnea long before rales become audible. Prompt treatment will prevent the grosser consequences of such failure. It must be the aim of treatment to maintain a normal blood volume and prevent retention of fluid, just as much as to strengthen the cardiac contraction with digitalis.

There are many patients with severe heart failure who are brought out of the gravest distress, but who remain with some degree of failure unless and until they are completely dehydrated. With this their blood volume is restored to normal, and then the weakened heart is able to maintain a balanced circulation. Clinically we recognized this years before we were aware of the importance of the increased blood volume, and before the mercurial diuretics were available. In those days we used to try to achieve the same dehydration by withdrawing fluid from the serous cavities and the subcutaneous tissues. I recall patients in whom we would tap the right chest one day, the left chest the next day, then the peritoneal cavity and then recommence the cycle with the right pleura until no more fluid would run out. In other cases we employed Southey tubes with similar success.

The reverse side of the picture is the intolerance of patients with weakened myocardiums to rapid intravenous infusions or transfusions. Commonly acute heart failure results, from such sudden increase of blood volume.

With far advanced heart failure, a shock-like syndrome may supervene. The cardiac output is reduced to such an extent that marked peripheral vasoconstriction sets in to shunt the scanty blood flow to the vital organs. The radial pulse is very small, the extremities become cold (17). This same mechanism is responsible for the slight elevation in rectal temperature that is so common in severe heart failure (18). The diminution of the peripheral blood flow impairs heat dispersal from the skin and so leads to increase in body temperature, al-

though the skin temperature may be low. When serious heart failure persists for months or years cachexia may finally supervene. This is caused by prolonged faulty nutrition of the tissues and organs, resulting from the persistent inadequate blood flow.

We have been discussing one form of myocardial insufficiency in which impairment of the contractile power of the heart muscle underlies the cardiac disorder. Angina pectoris represents another form of myocardial insufficiency with an altogether different mechanism. Here we are not dealing with an inadequacy of the cardiac pump with all of its consequences. Even during the anginal seizure there is no disturbance of cardiac output, of pulse rate or of respiration. A very compelling type of pain, together with a sense of being unable to draw a breath arrest the patient but not the circulation. The ultimate mechanism of the syndrome of angina pectoris has not yet been unravelled, but it is apparent that it is related to an inadequate blood supply, and an anoxemia of the myocardium. Thus angina pectoris occurs when there is narrowing of the coronary arteries or of their ostia, when there is sufficient stenosis of the aortic valve to limit the coronary flow; or when as a result of anemia or artificial oxygen deprivation, there is marked anoxemia of the heart muscle. But oxygen lack provokes anginal pain or electrocardiographic changes only when the coronary arteries are already narrowed. It is striking that angina pectoris and congestive heart failure rarely occur simultaneously, and that when a patient with angina pectoris develops heart failure the anginal pain usually disappears.

Two basic elements are concerned in the development of anginal pain; the heart lesion and the reaction of the heart nerves that register pain and initiate various reflexes, one of which brings on spasm of some part of the coronary tree. One diseased branch of a coronary artery may be responsible for the anginal syndrome, although the other coronary arteries and the heart muscle may be normal. A very sharp reduction in blood flow to only a small portion of heart muscle, with intense local anoxemia, and possibly the local development of an irritative substance like the "P" factor of Lewis seems necessary to provoke anginal pain. Such conditions do not usually occur in congestive heart failure, so anginal pain is absent. A patient with anginal pain due to coronary artery sclerosis does not develop congestive failure until he has had one or more myocardial infarcts. The closure of the artery and destruction of tissue that is involved in the formation of such an infarct destroys the local mechanism of pain production, so anginal pain disappears, and the weakening of the myocardium that results from necrosis and fibrosis of heart muscle induces congestive failure.

Angina pectoris and congestive heart failure occur simultaneously when the coronary flow of an overloaded, enlarged heart is markedly impaired. It is encountered in advanced aortic stenosis in which the narrowed valvular channel has caused marked cardiac overstrain and enlargement as well as great restriction of blood flow before it reaches the mouths of the coronary arteries just beyond the narrowed aortic orifice. Patients with advanced hypertension and large hearts usually have coronary arteriosclerosis as well. In them, too, conditions favoring the appearance of heart failure and of angina pectoris are present, and

in them we meet with both conditions. Acute left ventricular failure with severe anginal pain is commonly encountered in these two conditions.

In the preceding discussion we have considered the mechanism and consequences of heart failure. Let us now shift to clinical considerations and review some problems of myocardial insufficiency which face the practising physician. What induces heart failure? In certain cases the cause is quite evident. Heart failure may follow a major cardiac infarction that destroys and damages so much of the heart muscle that its pumping capacity is impaired. A true myocarditis such as occurs in rheumatic fever, or in diptheria may act in the same manner. The heart failure of acute nephritis is caused by diffuse myocardial injury that results from damage of the smaller branches of the coronary arterial system. These are all instances of widespread myocardial damage from intrinsic myocardial disease that interferes with the contractile power of the heart.

The normal heart rarely, if ever, becomes insufficient because it is overtaxed. Under circumstances of maximal physical exertion the voluntary muscles, and other body mechanisms give out before the heart begins to falter. But when a heart, damaged by valvular or myocardial disease, or laboring under the handicap of a severe anemia or a vitamin B deficiency is subjected to unusual strain, myocardial insufficiency may be provoked. It is not uncommon for a patient with chronic rheumatic valvular disease to experience the first evidences of heart failure after running up a flight of stairs, or after playing a set of tennis. The acute cor pulmonale results when a large pulmonary embolus places an unprecedented strain on the right ventricle.

The sudden onset of a very rapid heart rate, as in auricular fibrillation or in paroxysmal tachycardia is a common cause of heart failure. It is interesting to note that a heart otherwise normal will sustain such rapid rates for days or weeks without becoming insufficient. Younger persons with hyperthyroidism experience little distress if auricular fibrillation sets in. When the heart is enlarged, and embarrassed by a valvular defect or by myocardial scars, or overburdened by a high arterial tension, the onset of an irregularity such as auricular fibrillation precipitates acute heart failure.

But in most instances the onset of heart failure is gradual and insidious, and it becomes difficult to ascertain its exact cause. A patient has had hypertension or rheumatic valvular disease for years, and finally evidences of myocardial insufficiency begin to appear. They develop so gradually that the patient, at first, is hardly aware of their presence. Why has the heart become insufficient? If you will recall the dynamics and chemistry of the heart's action, it will be apparent that as the years go by a damaged and enlarged heart will gradually reach the limits of compensatory dilatation and hypertrophy and begin to flag under its constant excess load. In the case of a stenotic valvular orifice, the progressive narrowing of the ostium may become such an impediment to the blood flow that the circulation becomes insufficient while the myocardium is still strong. But in most instances, aside from the actual magnitude of the anatomic lesion, the duration of compensation depends on the balance of a number of factors in the patient's daily life. The most important of these are physical

activity (and here sudden spurts of strenuous exertion are more harmful than long sustained moderate activity), the fluid intake, and the nutrition of the body. It is a significant observation that patients with hypertension who have sustained a cerebral vascular accident with hemiplegia, and persons with advanced rheumatoid arthritis, who often have advanced valvular heart disease rarely experience myocardial insufficiency. This is due, I believe, to the fact that the enforced immobility induced by these complications spares the heart and lessens its load. Long continued excesses, even if they be minimal, in any of these factors provide a constant overload and hasten the time when the heart can no longer adapt itself to its progressively increasing mechanical inefficiency. There are cardiac patients who think it salutary to drink 10 glasses of water a day, there are others who take several teaspoonsful of sodium bicarbonate daily, and so ingest a great excess of sodium. The doctor, unaware of these idiosyncracies wonders why heart failure sets in. In older patients with hypertensive or arteriosclerotic heart disease, and emphysematous lungs, recurrent attacks of bronchitis or bronchopneumonia commonly induce heart failure.

Although it is true that the physician cannot correct an anatomical deformity of the heart, and restore it to its normal state, except for ligation of the ductus arteriosus when this congenital anomaly exists, the treatment of patients with heart disease is one of the most grateful activities of the physician. The heart has such remarkable powers of recuperation and adaptation that if given half a chance it can continue to sustain the life of the patient in comfort for years. Although we cannot correct cardiac defects, we can adjust the lives of our patients so that the development of myocardial weakness may be long postponed. We must try to avoid the first attack of heart failure, for once the heart has become insufficient it never fully recovers. As is clear from our earlier discussion, the larger the heart, the closer it is to reaching the limits of its reserve, the more imminent is the danger of myocardial failure. The larger the heart, the more carefully do we have to supervise our patients. While insisting on the need for guiding our cardiac patients, and planning their lives with them, I am the last to magnify their disabilities and to encourage them to adopt an attitude of invalidism or semi-invalidism. Common sense based on a knowledge of cardiac physiology is what is needed.

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THE ELECTROENCEPHALOGRAM IN SUBARACHNOID HEMORRHAGE

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The term subarachnoid hemmorrhage as used in this contribution designates massive extravasation of blood into the subarachnoid space caused by rupture of a congenital or acquired arteriosclerotic aneurysmal dilatation of a cerebral vessel or provoked by trauma causing laceration of blood vessels. The clinical signs and symptoms of subarachnoid hemorrhage are many and variable (1). Some cases show meningeal signs, others focal signs, some a combination of the two and an occasional few neither meningeal nor focal signs. In addition, during the clinical course neurologic and systemic manifestations may develop and disappear (1). This arouses the question as to the *modus operandi* of the blood in the subarachnoid space in the production of signs and symptoms (2). With this object in view, the electroencephalogram (EEG) was utilized in an attempt to gain some insight not only into the pathological nature of the effects of blood in the subarachnoid space but also as to the mode of production of such EEG abnormalities and the existence of any correlation between the two. In such a study some of the questions presenting themselves are: a) are the changes in the electroencephalogram due to the presence of blood in the subarachnoid space acting as a foreign body and thereby producing cortical irritation, b) are the changes in the electroencephalogram caused by the decomposition products of the blood acting as toxic chemical agents, c) are the changes in the electroencephalogram dependent upon a time interval elapsing following the onset of the subarachnoid bleeding, d) what is the mode of production of focal and of diffuse EEG abnormalities and finally e) of what clinical and diagnostic value is the EEG in cases of subarachnoid hemorrhage? To answer some of these questions an attempt was made to correlate the clinical and EEG findings in twenty-nine cases of subarachnoid hemorrhage.

TECHNIQUE

Standard records were taken with a three channel Grass electroencephalograph, using the following eleven electrodes: one vertex electrode (placed in the midline halfway between the nasion and inion); two "indifferent" electrodes (placed on the right and left ear lobes); four pairs of symmetrical electrodes above the hemispheres, namely two frontal electrodes (placed half the distance between the nasion and vertex and 3 cm. on either side of the midline), two central electrodes (placed 3 cm. lateral from the vertex electrode), two parietal electrodes (placed 4 cm. behind the vertex and 7 cm. on either side of the midline), two occipital electrodes (placed 3 cm. in front of the inion and 3 cm. on either side of the midline).

Records from symmetrical electrodes were taken simultaneously and the following leads were used: fronto-occipital; fronto-indifferent; centro-indifferent; parieto-indifferent; occipito-indifferent; fronto-vertex; centro-vertex; parieto-vertex; occipito-vertex; fronto-central; centro-parietal; parieto-occipital.

The records were grouped with some modifications according to the method previously described by Strauss (3). Before proceeding further, the following terms should be defined: high abnormality (H), low abnormality (L), E.E.G. focus (f), diffuse (d), asymmetrical (A), parasymmetrical (P), symmetrical (S), delta quotient, and bursts (B). A high abnormality record (H) is one in which the lowest frequency is 2 cycles per second, the average delta index 20 or more, and the delta index in one lead at least 35. A low abnormality record (L) is one in which any one of these conditions is not fulfilled. A symmetrical record (S) is one in which the delta activity is identical on both sides as to frequency, voltage and time of appearance. The term delta quotient means the figure obtained by dividing the sum of the delta index values of the higher abnormal side by the corresponding sum of the other side. Records with a high degree of abnormality are considered as asymmetrical (A) when the delta quotient is higher than 1.5, and are considered as parasymmetrical (P) when the delta quotient is 1.5 or less. In records with a low degree of abnormality, asymmetry (A) is characterized by a delta quotient higher than 2, and parasymmetry (P) by a value of two or less. The letter "d" denotes a diffusely abnormal record without any focal accentuation. The letter "f" indicates focal accentuation in the electroencephalogram. Bursts (B) are defined as a series of waves (three or more) having a frequency of 3–6 per second and an amplitude of at least 20 microvolts. If the series consists of two waves they must at least equal in amplitude the alpha activity.

RESULTS

For purposes of classification we will consider our cases as belonging in any one of the four clinical categories: (1) those presenting a meningeal syndrome only, (2) those with focal and meningeal signs, (3) those with focal signs only, and, finally, (4) those with neither focal nor meningeal signs. The diagnosis of subarachnoid hemorrhage was confirmed in all the cases by the presence of blood in the spinal fluid.

CASES PRESENTING A MENINGEAL SYNDROME ONLY

The symptoms and signs of meningeal irritation consisted of the following: headache, vomiting, disturbance in consciousness, neck rigidity, positive Kernig sign, and temperature elevation. Less constant symptoms and signs included cranial nerve palsies, papilledema with or without retinal hemorrhages, anisocoria, convulsions, a positive Babinski reflex, and bradycardia. Eighteen patients presented clinically a meningeal syndrome only. Of these eighteen patients, six had normal records, nine showed a low degree of diffuse abnormality, two a high degree of diffuse abnormality, and the remaining one had a record showing a high degree of diffuse abnormality with a focus, despite the clinical absence of focal signs or symptoms. However, a subsequent record of this last patient taken fifteen days later failed to show the focus, but did continue to show a high degree of diffuse abnormality (fig. 1).

Of the six normal records, one was taken on the third and one on the sixth day of the illness, with blood in the spinal fluid and in the presence of meningeal signs and symptoms. Of the remaining four normal records, one was taken on the eighth, one on the 19th, one on the 28th and one on the 43rd day of illness. All patients were asymptomatic at that time and only in the case recorded on the 43rd day of illness was there a spinal fluid examination made at the time of recording, and that fluid was xanthochromic.

The eleven diffusely abnormal records were taken at varying intervals from the 4th to the 23rd day of illness. One patient showed meningeal signs and gross

blood in the spinal fluid at the time of recording, one showed meningeal signs and xanthochromic fluid at the time of recording, two showed xanthochromic fluid but were asymptomatic at the time the EEG was taken. The remaining seven patients showing diffusely abnormal records did not present any meningeal signs, nor was there any spinal fluid examination made at the time of the recording.

One patient whose record was taken on the eighth day of illness with blood in the spinal fluid and signs of meningeal irritation only, showed a focus of high abnormality in the electroencephalogram. However, this same focus

	DAY OF ILLNESS													
	3rd	4th	6th	8th	9th	10th	14th	17th	18th	19th	23rd	28th	43rd	44th
15 cases with single records	N (s1)		N (s1)	N (n4) LP-d (n4)	LS-d (n2)	HP-d (n4) LS-d (s2)	LS-d (n4)	LS-d (s4)	LS-d (n4)	N (n4) HP-d (n2)	LP-d (n4)	N (n4)	N (n2)	
Case a: 3 records				HA-f (s1)							HS-d (n4)			N (n4)
Case b: 2 records		LP-d (s1)						N (n4)						
Case c: 2 records					LS-d (n4)					N (n4)				

FIG. 1. Cases presenting a meningeal syndrome only

Spinal fluid at the time of EEG recording. 1. bloody, 2. xanthochromic, 3. clear, 4. no spinal fluid examination at the time of EEG examination.

Clinical signs at the time of EEG recording. s. meningeal signs, n. no meningeal signs, F. focal signs.

EEG signs. N. normal record, L. low abnormality, H. high abnormality, S. symmetrical, A. asymmetrical, P. parasymmetrical, d. diffuse, f. focal, B. bursts.

disappeared on reexamination 15 days later, when the patient was asymptomatic, and was replaced by a diffuse abnormality. No spinal fluid examination was made at this second recording.

Repeated EEG examinations on three (a, b, c) of the 18 cases showed a progressive diminution in the degree of abnormality with the lapse of time.

CASES PRESENTING MENINGEAL PLUS FOCAL SIGNS

Five patients clinically showing focal as well as meningeal signs also exhibited at one time or another a corresponding focus in the electroencephalogram. In one case (d), recorded on the 15th day of illness with clear spinal fluid and focal

symptoms only, the electroencephalogram showed a focus. However, in a second record taken 18 days later with the clinical focus still present, the electroencephalographic focus had disappeared. In another case (e), the electroencephalogram was taken on the 23rd day of illness, with both meningeal and focal clinical signs present, and was diffusely abnormal. A subsequent record of this same case (e) taken on the 37th day of illness showed a focus corresponding to the clinical focus. At no time in this case was a spinal fluid examination made at the time of recording. Repeated electroencephalograms taken on four (d, e, f, g) of the five patients showed a progressive diminution in the degree of abnormality with a corresponding lapse of time (fig. 2).

CASES PRESENTING FOCAL SIGNS ONLY

The EEG records of these two patients were both abnormal. In one patient (h) the record was taken on the second day of illness with blood in the spinal fluid and a clinical focus present. It showed a corresponding focus in the EEG.

	DAY OF ILLNESS								
	5th	8th	15th	23rd	28th	33rd	37th	46th	200th
Case c′					LA-f (Fn4)				
Case d			HA-f (Fn3)			LA-d (Fn4)			
Case e				HP-db (Fs4)			HP-f (Fn4)	LP-f (n4)	
Case f	HA-f (sF2)			LA-f (F3)					N(n4)
Case g		HA-f (sF4)				N(n4)			

Fig. 2. Cases presenting meningeal plus focal signs

For explanation of symbols see legend accompanying fig. 1

Subsequent records of this same patient taken on the 20th and 40th days of illness showed a diffuse one-sided abnormality, the degree of abnormality diminishing with the lapse of time. No spinal fluid examination was made at the second or third recordings but the clinical focus was still present. In the second case, the EEG was recorded on the sixth day of illness and showed no focus, but was diffusely abnormal despite the presence of a clinical focus. Here too, no spinal fluid examination was made at the time of the EEG recording (fig. 3).

CASES PRESENTING NEITHER FOCAL NOR MENINGEAL SIGNS

Four patients presented neither focal nor meningeal signs. In one of these patients the EEG was taken on the eighth day of illness in the presence of xanthochromic spinal fluid and was normal. Records of the remaining three patients taken on the first, second and ninth days of illness, respectively, all

showed diffuse EEG abnormalities, one patient had blood in the spinal fluid, one xanthochromic fluid and in the third patient no fluid examination was made at the time of the recording. Repeated EEG records were taken in two of the patients (i, j) after a variable lapse of time of from one to thirteen days and both showed a progressive diminution in the degree of abnormality (fig. 4).

COMMENT

Many cases of subarachnoid hemorrhage show normal electroencephalograms although the spinal fluid is bloody and meningeal signs are present at the time of the recording. We have seen this same phenomenon occur in states of men-

	DAY OF ILLNESS			
	2nd	6th	20th	40th
Case h	HA-f (F1)	HP-d (F4)	HA-d (F4)	HA-d* (F1)

* Though this still shows a high degree of abnormality, it is less abnormal than the one recorded on the 20th day of illness.

Fig. 3. Cases presenting focal signs only

For explanation of symbols see legend accompanying fig. 1

	DAY OF ILLNESS						
	1st	2nd	8th	9th	10th	11th	22nd
Case i	LS-d (2)	LP-d (1)	N (2)			LP-d* (4)	
Case j				HP-d (4)	LP-d (4)		N (4)

* Lesser degree of abnormality than in the first electroencephalogram.

Fig. 4. Cases presenting neither focal nor meningeal signs

For explanation of symbols see legend accompanying fig. 1

ingeal irritation due to various other causes, e.g. bacterial meningitis. On the other hand, definitely abnormal electroencephalograms have been recorded in cases with a similar symptomatology and such abnormalities have persisted even after the menigeal syndrome had disappeared (cf. case a). For these observations we have no explanation to offer. Savitsky and associates have paid attention to the time factor and stated that the electroencephalographic abnormalities in cases with subarachnoid hemorrhage are due not solely to the mechanical effect or the pressure of the blood upon the brain but to anatomic

changes in the cortex (seepage of blood, disintegration), as described earlier by Strauss, Globus and Ginsburg (1). Their opinion is based upon the observation of a patient in whom the degree of diffuse abnormality of the electroencephalographic recording increased for some time after the hemorrhage without evidence of increased intracranial pressure or repeated bleeding. Our material shows that such an increase of abnormality is certainly not the rule. All our cases with repeated records showed a gradual decrease in electroencephalographic abnormality and the series as a whole does not present a curve demonstrating an increase of abnormality with a subsequent decrease. We feel, therefore, that the occurrence of cortical changes cannot be postulated as being the main basis for the electroencephalographic abnormalities in cases of subarachnoid hemorrhage. In any case, one has to consider the possibility that diffuse electroencephalographic abnormalities may be due to a dysfunction of the deeper centers close to the third ventricle and not to diffuse damage to the cortex itself. The deep centers may be easily affected in cases of subarachnoid hemorrhage since many such hemorrhages arise from vessels at the base of the brain. Whatever the cause of the electroencephalographic abnormalities, it is interesting to note the differences in various cases presenting similiar clinical pictures and the long persistence of the electroencephalographic abnormalities in some. These facts cannot as yet be adequately explained and present problems for further research.

An electroencephalographic focus was found in seven cases. In only one of these cases (a) no focal signs were present on clinical examination. However, the electroencephalographic focus in this particular case was no longer present when a second recording was made two weeks later. In such cases further observations should show whether some focal lesion (e.g. bleeding hemangioma) is present, despite the absence of corresponding clinical signs. In the other six cases with an electroencephalographic focus a corresponding clinical focus was present. The EEG in these cases is similar to those recorded in brain tumors. However, in all these cases repeated electroencephalograms showed a decrease in the degree of abnormalities, an observation not found as a rule in brain tumors. In three cases the electroencephalograms were repeated at successive intervals until they were found to be normal again. This observation may offer an aid in the differential diagnosis between a bleeding cerebral tumor and a subarachnoid hemorrhage due to some other cause.

SUMMARY

Twenty-nine cases of subarachnoid hemorrhage were studied in an effort to correlate the electroencephalogram with the clinical findings.

A correlation was found to exist between clinical cortical foci and focal abnormalities in the electroencephalograms.

Neither the presence of blood in the spinal fluid nor the presence of meningeal symptoms bears any relation to the electroencephalogram.

In all cases the degree of abnormality in the electroencephalogram showed a

progressive diminution when repeated examinations were made at increasing intervals of time.

No increase in the degree of electroencephalographic abnormality was noted in subsequent records once the hemorrhage had ceased.

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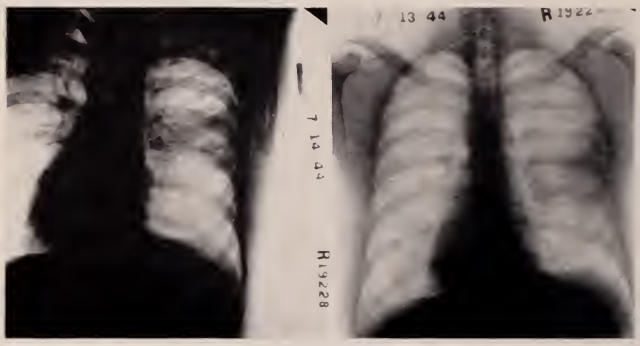
THE LATERAL DECUBITUS POSITION IN X-RAY EXAMINATION OF THE CHEST

SAMUEL RICHMAN, MAJOR, M.C., A.U.S.

Roentgen examination of the chest in the lateral decubitus position has been a well known procedure among radiologists for many years. Its ability to yield valuable information in diseases of the pleura (effusion, thickening etc.) and lungs (cavitation, etc.) is generally appreciated among the specialists in the field. Rigler (1) was among the first to expound its value, especially in the diagnosis of small pleural effusions. The purpose of this communication is to emphasize the advantages of this position to the military personnel not specializing in radiology as well as to the civilian general practitioner. The lateral decubitus position is of particular value: 1) When it is desirable to demonstrate a fluid level in the chest in patients who are too weak to assume an upright posture. In fact, in no other manner can the presence of the fluid level be established, either in the pleural cavity or in the lung itself, in a patient who cannot be placed in the upright position. Incidentally, the left decubitus position, with the right side up may also be used to determine the presence of free air under the diaphragm in cases of suspected perforated peptic ulcer etc. 2) To differentiate the character of the effusion in the pleural cavity. Usually there is a shift in the position of the fluid when the patient is turned on his side. Rigler states "The cases in which no change in position of the fluid occurs are invariably exudative in type; they are either of long standing so that adhesions have formed, or of more recent origin with pus of a thick fibrinous character." 3) In females where the breast tissue frequently obscures the lower lung fields especially the costophrenic sinuses. This position causes a shifting of the overlying soft tissue shadows, muscle and subcutaneous, so that lung details may be more clearly made out. By comparing a film taken in the lateral decubitus with that done in the usual upright position, the persistence or non-persistence of shadows may be of considerable aid in the differential diagnosis. 4) In the presence of fluid in the pleural cavity, the position and appearance of the diaphragm can be more easily made out than in the upright film. 5) In the group of patients in which the fluid in the pleural cavity presents an atypical appearance in the upright position. The most common type in this group is that in which the upper surface of the fluid is flat instead of the usual curved line extending upward along the lateral chest wall. The lateral decubitus film will usually show the fluid to shift and thus will aid in eliminating the possibility of other conditions. 6) To furnish greater detail of the pathological change in the lateral peripheral (axillary) portion of the lung. Due to the crossing of the ribs in this region, fine lung detail is difficult to distinguish. In the lateral decubitus position the shift of the mediastinum and the lung tends to bring into view more of the lateral peripheral lung area, thus enabling one to see more clearly any change occurring there.

Illustrative of the value of the lateral decubitus position is the case in which

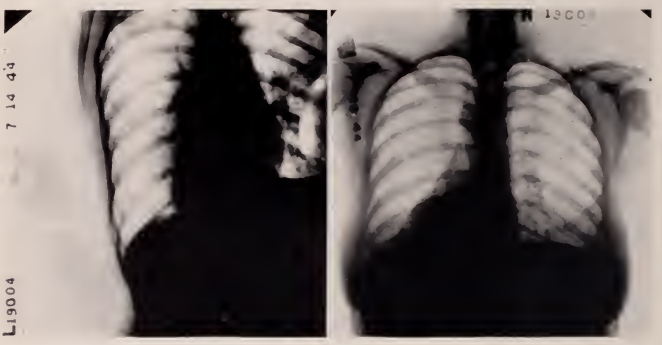
an ordinary upright film of chest revealed a more or less homogeneous density in the mid-axillary portion of right chest. It was difficult to ascertain whether or



b a

Fig. 1. (a) There is an indefinite triangular area of increased density in the mid-right chest. Differentiation between pulmonary infiltration and pleural exudate or both is very difficult.

(b) Lateral decubitus roentgenogram shows clearly that at least part of the process is due to pleural thickening or exudate.



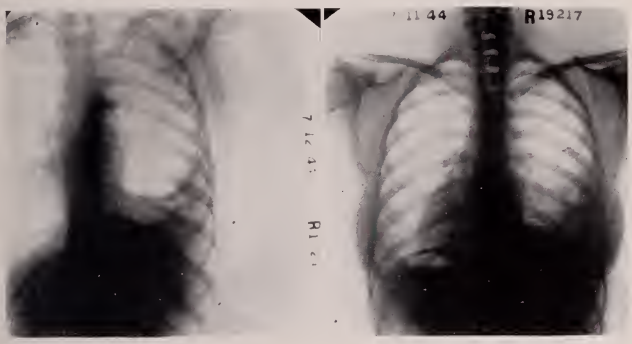
b a

Fig. 2. (a) The left base is obscured by an indefinite haziness as well as linear densities suggesting fibrous strands.

(b) A roentgenogram made in the lateral decubitus position with the right side of the chest on the table shows a clear costophrenic sinus.

not pleural involvement, in addition to that of the lung, was also present. The left decubitus film clearly shows the sharp straight line along the lateral chest

wall suggestive of pleural thickening (fig. 1). Another case is that of a female whose upright film of the chest showed some thickening and fibrous strands in the region of left base. Overlying breast tissue obscured details of the appearance of the diaphragm and costophrenic sinus. The lateral decubitus film, with the left side up, clearly demonstrated the smooth rounded contour of the diaphragm as well as a normal costophrenic sinus (fig. 2). To demonstrate the encapsulation of fluid within the pleural cavity, the lateral decubitus position will not only show no shift in the shadow seen in the upright film but in addition will bring out more clearly the findings already noted (fig. 3).



b a

Fig. 3. (a) The lower fourth of the right chest is obscured by a homogeneous density. (b) A roentgenogram made in the lateral decubitus position reveals encapsulation of fluid in the lateral portion of the chest. There has been no shift with change in position of the patient.

TECHNIC

The lateral decubitus position may be taken with either the right or left side down, and with the film placed in front of the patient a regular posterior-anterior view of the chest is made. In my experience, it is usually best to place the involved side of the chest uppermost, although in some cases as in the presence of free fluid in the pleural cavity, the reverse is more desirable.

SUMMARY

1. The lateral decubitus position in x-ray examination of the chest is a valuable aid in the differential diagnosis of lesions within the chest.

2. It is suggested that the lateral decubitus position of the chest be used more frequently, especially in cases of suspected disease in the region of the diaphragm and costophrenic sinus.

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COMBINED ILEO-VESICAL AND SIGMOIDO-VESICAL FISTULA SECONDARY TO DIVERTICULITIS

Case Report

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The literature on the subject enterovesical fistula secondary to ruptured diverticulitis of the colon is considerable, but the condition is sufficiently uncommon to justify the report of a case.

CASE REPORT

History. (Adm. #541238). This was the first admission to The Mount Sinai Hospital of a 50 year old man. The patient complained of intermittent left lower abdominal quadrant pain, diarrhea, burning micturition, pneumaturia and the occasional passages of feces through the urethra.

At 38 years of age, he had an acute episode of right lower abdominal pain with diarrhea and vomiting, which subsided subsequently without treatment. Nevertheless, he went to a hospital where a routine appendectomy was performed. He was told at that time that he had chronic appendicitis. His post-operative course was uneventful. He was well subsequently until the age of 45 years, when he began to experience intermittent lower abdominal cramp-like pain which subsided without treatment. Two years later, these pains became severe and frequent, and were accompanied by profuse diarrhea. He consulted a physician and an x-ray examination of the gastrointestinal tract was performed. The examination revealed a sinus tract between two loops of intestine. Two years later, in October, 1944, he began to experience pain over the bladder and urethra during micturition, with the passage of cloudy urine. The patient consulted a urologist, who carried out a cystoscopic examination which disclosed no abnormalities of the bladder. He was treated with sulfonamides without improvement.

One month later, the patient began to pass fecal material through the urethra. He consulted a physician who told the patient that such a condition "does not exist". Six months later he began to have chills and fever with aggravation of the urinary symptoms. He consulted another urologist who found the bladder and prostate to be the seat of an acute inflammation. At that time, x-ray examination was again performed and the diagnosis of a sigmoido-vesical fistula was established. The patient was admitted to The Mount Sinai Hospital for surgical treatment.

Examination. The patient was well developed and well nourished. The lungs were clear. The heart was not enlarged. The systolic blood pressure was 154 mm. Hg. and the diastolic, 104 mm. Hg. The abdomen showed a well healed scar. A definite tender palpable mass was present in the left lower quadrant. The rectal examination was negative.

Laboratory Data. The blood examination showed hemoglobin, 96 per cent; white blood cells, 10,500; polymorphonuclear leucocytes, 65 per cent; lymphocytes, 31 per cent; (nonsegmented, 3 per cent); eosinophiles, 1 per cent. Urinanalysis showed a trace of albumin and a few bacteria. X-ray examination of the intestinal tract following a barium enema revealed diverticulitis of the sigmoid with constriction of the lumen and several diverticula in the descending colon. The area of diverticulitis appeared to be adherent to the bladder.

Course. Sulfadiazine was administered forty-eight hours before and after each stage of surgery. Free bladder drainage was established by an indwelling catheter. The first operation was performed on November 1, 1945; the abdomen was opened through an upper right rectus incision. An inflammatory mass was found in the left lower quadrant adherent

to the bladder. The transverse colon was exteriorized and a double barrelled colostomy was performed. The colostomy functioned well. The urine became clearer and the subjective urinary symptoms subsided promptly. At this time the urine still contained some bacteria and yeast cells.

The second operation was performed on November 19, 1945. Some adherent omentum was freed from the abnormal tissue to reveal the fixation of the urinary bladder to the sigmoid and distal ileum. Two fistulae were demonstrated, one between the sigmoid and the left cornua of the bladder and the second between the distal ileum and the upper posterior wall of the bladder. The sigmoido-vesical tract was cut through to free the sigmoid, as was also the fistula between ileum and bladder. The bladder openings were closed in two layers. The opening in the ileum was similarly repaired. The segment of diseased sigmoid was then resected between rubber-covered clamps and an end-to-end anastomosis was performed. Five grams of sulfanilamide powder were dusted into the wound and the abdomen was closed in layers. During the operation the patient received 500 cc. of citrated whole blood.

The post-operative course was quite uneventful. The operative wound healed by primary union. The indwelling bladder catheter was removed on the sixth post-operative day. The bladder was irrigated daily with acriflavine solution 1:4000. A urine specimen on the seventh postoperative day was free from bacteria and yeast cells. At this time there were no urinary symptoms.

The pathological examination of the excised intestinal tissue showed an abundant amount of pericolonic fat tissue which was firm and infiltrated in places. The muscle coat was greatly thickened. The mucosa was gray, thrown up in folds. The previously described firm area (the size of a small walnut) in the pericolonic fat tissue was situated in the middle of the specimen and appeared to surround a fistulous tract leading from the colon to an opening about 2.5 cm. distad. There was a diverticulum of the mucosa which had a depth of 1.5 cm. in the vicinity of the first lesion. The previously described fistulous tract was lined by colonic mucosa. On cutting the subserosal fat tissue, three more diverticula which were not visualized previously were encountered. They were not inflamed. Microscopic examination of the specimen showed chronic and acute diverticulitis.

The third stage of the operation will consist of extraperitoneal closure of the colostomy.

COMMENT

Reference to the literature reveals that vesico-intestinal fistulas are uncommon but not rare. The preponderence of the cases reported describe fistulae between the large bowel and the bladder with a lesser number involving the small bowel. The combination of the two conditions seldom occurs.

The most common cause of vesico-colic fistula is diverticulitis of the colon. In fact, in a collected series of 328 cases reported by Higgins (1) an inflammatory lesion was the etiologic factor in 160 cases and diverticulitis was the initiating cause in 57.5 per cent. Dobson and Moir (2) collected 46 cases of vesicointestinal fistula, of which 30 cases were secondary to diverticulitis of the colon. Rusche and Bacon (3) stated that diverticulitis accounts for approximately 50 per cent of all cases on record. In a series of cases reviewed by Forbes (4) diverticulitis of the sigmoid was found to be the etiologic factor in 42 per cent of the cases of vesico-intestinal fistulas. Kellogg (10) in 1938 discussed the condition in detail and summarized 592 cases reported until that time. 42 per cent in this series were secondary to diverticulitis of the colon. Gouverneur (5) found 38 fistulas representing 11 per cent of 324 cases of diverticulitis.

The pathologic sequence of events culminating in entero-vesical fistula due to diverticulitis may be reconstructed in the following manner:

The general picture is that of a peridiverticulitis and local peritonitis with secondary adhesions between the intestine and the dome of the bladder. As the inflammation progresses, more structures may become adherent and an abscess may form. The wall of the bladder becomes reddened and edematous and finally ulceration goes on to perforation.

Although slight variations due to the location of the primary lesion may be present, the general syndrome presented by patients with enterovesical fistula is fairly constant. As a rule they state that the condition was gradual in onset. Repeated attacks of lower abdominal, cramp-like pain, left hypogastric tenderness, change in intestinal habits, namely intermittent diarrhea or constipation, or an alternation of both; later burning and frequency of urination occur. Chills and elevation of temperature complete the syndrome.

With the establishment of a fistula into the bladder, air may be passed through the urethra, usually at the end of micturition, but the passage of feces does not occur as frequently as does that of flatus. Pneumaturia, although helpful in the diagnosis of fistula, is not pathognomonic. In fact, the passage of gas through the urethra may be due to catheterization, fermentation of urine in the bladder by yeast organisms, and to occasional cases of chronic infections of the renal pelvis or the bladder due to the Escherichia coli, Aerobacter aerogenes, or coccobacillus vesicae (6, 7).

The actual demonstration of the fistula by means of x-ray examination and barium enema, may be difficult but should be possible if the opening is of sufficient size. It rarely is possible to find the opening in the intestine by means of sigmoidoscopy (8).

Cystoscopic examination may be of some diagnostic value, when associated with the previously described symptoms. The appearance will be that of an area of edema and inflammation in the fundus of the bladder.

A survey of the existing literature yields a number of methods used in the surgical treatment of entero-vesical fistula due to diverticulitis (9). The three chief methods of approach are: 1) colostomy or cecostomy alone, 2) a single stage procedure with or without the establishment of a proximal colostomy, 3) a multiple stage procedure.

Experience has shown that the three stage operation has much to commend it and will probably be the operation of choice in most instances. The first stage consists of a complete diverting proximal colostomy. The major operation is carried out three weeks later and consists of separation of the diseased bowel from the bladder, repair of the bladder fistula and resection of the diseased segment of colon. The final stage is an extra peritoneal closure of the colostomy. The results following this staged operation have been excellent.

Drainage of the urinary bladder following the second stage is essential. This may be achieved by either a suprapubic cystotomy or an indwelling urethral catheter.

SUMMARY

This report has presented a combined ileo-vesical and vesico-sigmoidal fistula secondary to diverticulitis of the sigmoid. The entire syndrome of the entero-vesical fistulas has been reviewed.

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ESSAYS ON THE BIOLOGY OF DISEASE[1]

ELI MOSCHCOWITZ, M.D.

Chapter 14

EMPHYSEMA

While emphysema has had adequate study, the conclusions lack not only unanimity but correlation, because the malady has been largely studied from the static rather than the biological viewpoint. It is interesting to note, as a corroboration of this thesis, that some active students of the disease have completely reversed their stand as the result of more prolonged observation.

Varieties: A large number of acute emphysemas are *compensatory* or perhaps better termed *complementary*, sequential to a greater or lesser involvement of thoracic space by pneumonia, atelectasis, pleural exudates, etc. These are transient and subside completely when the primary process has disappeared. On the other hand, if a considerable portion of the chest space has been compromised by a chronic process, for instance, tuberculosis, pulmonary fibrosis from excessive radiation, pneumoconiosis, non-malignant pulmonary or pleural neoplasms, extensive brochiectasis, bilateral and extensive pleural adhesions, etc. a permanent emphysema develops which may lead to a hypertension of the pulmonary circuit, precisely comparable to that conventionally noted in the commoner obstructive variety of emphysema.

The emphysema that arises in prolonged mountain sickness may also be regarded as compensatory to the anoxemia (1). This has been reproduced in animals by prolonged exposure to low oxygen tensions (2).

There is a transient emphysema that occurs occasionally in children with pertussis, due, in all probability, to violent coughing and the excessive activity of the normal and accessory muscles of respiration which expand the chest wall (3).

Whether a chronic bronchitis may give rise to a permanent emphysema by the same mechanism seems very likely, if one may judge from the sequence of clinical events. An added factor may be the narrowing of the respiratory passages from the swelling of the mucosa. I have noted the development of emphysema on a number of occasions as the result of chronic cigarette cough. On the other hand, a chronic bronchitis often follows an emphysema, so that this common association may be both a cause and effect.

The *senile* variety of emphysema is regarded by most observers as a distinct type, secondary to senescent changes in the thoracic cage. Freund (4) ascribed the primary lesion to ossification of the costal cartilages. Kountz and Alexander

[1] This is the fourteenth chapter in a series of essays by Dr. Eli Moschcowitz, in which an attempt will be made to interpret certain forms of chronic disease from the biologic viewpoint, as opposed to the current trend toward rigid classifications implying a concept of disease as a more or less static phenomenon.

According to present plans, these essays will appear in consecutive issues of the Journal of The Mount Sinai Hospital. When the publication of the projected series of essays is completed, the several installments will be assembled and printed as a monograph.—Ed.

(5) believe the barrel chest results from a primary disease of the intervetebral disc which at first straightens the dorsal spine and later results in a kyphosis. Kerr and Lagen (6) described a form of emphysema occurring in the 5th and 6th decades that follows a postural syndrome due to obesity and a pendulous abdomen. Changes in the dorsal spine result with flaring of the ribs and the formation of a barrel chest. There is therefore evidence that a type of emphysema, senile if one may call it, that is secondary to disease of the bodily framework. In this sense, this type may also be regarded as compensatory. To be sure, Tendeloo (3), a persistent student of the disease, denies such a genesis, and holds that the primary change is a loss of pulmonary elasticity incident to age, and that the changes in the framework are subsidiary. This will be discussed later. In senile emphysema, the lungs are small and collapse when the thorax is opened in contrast to the obstructive type. Clinically, senile emphysema is fairly innocent during a larger part of its course. The oxygen saturation is normal and there is no retention of carbon dioxide; the diaphragm retains almost its normal excursion and breathing is largely abdominal. The heart remains normal in size, unless complicated by an associated hypertension or myocardial disease. Even in uncomplicated senile emphysema hypertension of the pulmonary circuit may follow. This eventuality is infrequent because the patient first succumbs to another senile disorder.

The most common variety is the *obstructive* type. This follows any disorder in which expiration is hindered, most frequently bronchial asthma, less frequently obstructive lesions of the bronchi due to neoplasms (usually adenoma), mediastinal tumors, aortic aneurysm, chronic bronchitis and obstructive lesions of the larynx. This type can be reproduced experimentally by obstructing the trachea with a brass tube containing a valvular attachment (7, 8). In obstructive emphysema, the lung is voluminous, and does not collapse when the chest is opened, due to loss of elasticity. The lobules are larger and often fuse together by rupture of the intervening septa (9). The terminal bronchioles are dilated, the lung is pale in the early phase due to extensive obliteration of capillaries.

Microscopic pathology. In obstructive emphysema this varies profoundly depending on the stage of the process. In the early stages, before any degree of hypertension of the pulmonary circuit has arisen, the alveoli are much distended, the walls are thin and many of the capillaries are obliterated. The elastic tissue is frayed and broken. When hypertension of the pulmonary circuit supervenes, dilatation of the remaining capillaries ensues with progressive productive changes in the walls of the alveoli, so that they become thickened, often with hyalinization. (10). The lung now presents the morphology of brown induration.

Pathological physiology. In obstructive emphysema the chest has the characteristic barrel shape, but this deformity is now secondary and not primary as in the senile and postural varieties. The diaphragm is pushed downward and its excursions are diminished. The chest is thus maintained in a greater or lesser inspiratory position. The heart often assumes the configuration of the "drop heart" in the earlier stages, before hypertension of the pulmonary circuit and heart failure have set in. Breathing is largely carried on by intercostal and

accessory muscles of respiration together with the abdominal; as a consequence these muscles and especially the abdominal often reveal a striking hypertrophy in obstructive emphysema. At the same time, intraabdominal pressure increases and it is presumed that, by pressure upon the abdominal veins, the return flow of blood to the heart is impeded. This may account in part at least for the relief patients derive from an abdominal belt which facilitates the venous return.

In the course of the maturation of the emphysema, a host of other factors participate.

a. *Loss of elasticity.* Henneman and Metz (11) measured the elasticity of segments of normal lungs and found a progressive increase up to the 20th year. After the 25th year there was a progressive decrease, which they and Tendeloo (3) regarded as provocative of the senile type. They also measured segments of lungs of the obstructive type and found a loss of elasticity greater than the age demanded. Christie (12) showed convincingly in the living subject, by simultaneous measurements of the intrapleural pressure and the tidal air, a profound to almost a complete loss of elasticity in obstructive emphysema. This loss of elasticity brings in its train important sequelae. Normal expiration which is largely a function of the pulmonary elasticity and is passive, is replaced by active muscular effort. Respiration is further impeded because the chest wall is already in the state of deep inspiration and the excursions of the diaphragm are small. In addition, Christie presents evidence that "the peripheral distended and relatively ischemic alveoli are over ventilated at the expense of the deeper and more normal alveoli. The subsequent diminution of the effective tidal air is responsible for some if not all of the anoxemia and CO_2 retention observed in emphysema." This explanation corresponds closely to that demonstrated by Haldane (13) many years ago. A further consequence of the loss of elasticity is the tolerance such patients evince to spontaneous and artifial pneumothorax.

b. *Changes in intrapleural pressure.* The progressive loss of pulmonary elasticity after the 20th year demonstrated by Henneman and Metz (11) are somewhat paralleled by the observations of Prinzmetal and Kountz (14) who found during the fourth decade both a reduction of vital capacity and in the ability of the individual to lower his intrapleural pressure. Kountz, Pearson and Koenig (15) found in emphysema that the intrapleural pressure was less negative than in normal individuals. This finding apparently represents a fixed stage of the identical change noted by Prinzmetal (2) during an asthmatic paroxysm, and affords another example of the transition from an exaggerated normal function to a fixation of that function, which we have termed "hyperkinesis" (16). Prinzmetal (2) demonstrated the same phenomenon in experimental bronchoconstriction.

c. *Venous pressure.* Kountz and his associates (8) found during an asthmatic attack and also in emphysema that the venous pressure rises more or less parallel to the rise in intrapleural pressure, due to interference with the venous return. That was also true in experimental emphysema. In asthma, the rise in venous pressure promptly returns to normal after the attack, but when emphysema is associated, the pressure dropped slowly, sometimes in the course of days. These

rises in venous pressure only exceptionally attain heights above the normal range in emphysema uncomplicated by heart failure, which is in accord with the findings of Weiss and Blumgart (17) who found the venous pressure normal in emphysema, except in "severe" instances. However, if patients with emphysema are followed over a sufficient span of time, a progressive rise in venous pressure is often noted pari passu with clinical evidences of an increase in intrapulmonary arterial pressure, such as increasing cyanosis, breathlessness and an increasing density of the pulmonary markings. Inasmuch as the transition from hypertension of the pulmonary circuit to right heart failure is a gradual one and inasmuch as normal venous pressure represents a range rather than a precise mathematical quantity, it is difficult to determine when, in emphysema, the rise in venous pressure determines the induction of heart failure. In time the venous pressure attains a height that definitely spells failure of the right heart. The venous pressure is one of the factors that determines the difference between mild and "severe" emphysema. The time element affords an explanation, in part at least, for the diverse venous pressures reported by different observers in emphysema. Obviously we are referring only to uncomplicated cases of obstructive emphysema. When a cardiac lesion is associated, an elevated venous pressure may arise through that agency alone.

d. *Circulation time.* Here as well, static measurements of the circulation time in emphysema have led to diverse interpretations. These afford at best only linear relationships. Weiss and Blumgart (17) in 33 patients with obstructive emphysema found the circulation time with the radium method normal in 29 and only moderately elevated in four. Indeed in some patients the circulation time was faster than normal. Even in severe cases, the circulation time was less then that witnessed in myocardial failure. These observations demonstrate "that even severe chronic emphysema does not necessarily obstruct the blood flow sufficiently to interfere with the normal velocity of blood flow through the lungs". They regard this increased velocity as an attempt to compensate for the insufficient ventilation. Tarr, Oppenheimer and Sager (18) in 19 patients using decholin found the circulation time normal in 13. In the remaining 6 it was prolonged up to 22 seconds. It is natural to infer that when a prolonged circulation time is found in emphysema that heart failure has set in. Indeed of the 6 cases of Tarr, Oppenheimer and Sager, four revealed clinical evidences of congestive failure, while in two it was absent. In any event, the mere circumstance that the circulation time in emphysema is sometimes normal and sometimes prolonged indicates that there must have been a transition period, but when heart failure entered cannot be determined by the circulation time alone, without taking other clinical data into consideration. In other words, a progressive rise in circulation time in emphysema indicates changes in dynamics that lead to heart failure but does not necessarily imply it.

The impression must not be gained that these abnormal functions that arise in the course of an obstructive emphysema can be divorced from each other. Not only is there a greater or lesser interplay but the precedence has not always been established. Above all, the time factor must always be introduced. The

summation of these abnormally acting forces in emphysema have profound effects upon the organism.

1. *Ventilation.* The vital capacity is consistenly reduced, although the total capacity is not changed. There is an increase in the residual air at the expense of the complemental and supplemental air (19). Hurtado and his coworkers (20) find that the ratio between the residual air and the total capacity affords a close correlation with the degree of respiratory disability, and is therefore useful in emphysema for diagnostic and prognostic purposes.

2. *Anoxemia.* In 24 cases of pulmonary emphysema Hurtado et al (20) found the oxygen saturation to vary between 72.9 and 97.7 per cent with a mean value of 88.2 per cent, a value definitely less than normal. In 20 cases it was below the normal limit, 94 per cent, and in 14 the saturation was less than 90 per cent. Meakins and Davies (21) found the saturation of arterial blood varied from 86 per cent to 90 per cent. Lemon's (22) average was about the same and varied between 84 and 89 per cent. Himwich and Loebel (23) reported the arterial oxygen saturation in three emphysematous patients. In two it was normal. In the third it averaged around 83 per cent; with slight exercise it sank to 23 per cent one to two minutes later. The comparatively wide range of arterial oxygen saturation again leads one to believe that there is a progressive loss with time and the intensity of the process.

The anoxemia is usually of sufficient degree to produce the characteristic cyanosis. Lemon (22) calculated that the degree of unsaturation of the capillary blood attains that formulated by Lunsgaard and van Slyke as necessary to produce cyanosis. Inasmuch as prolonged anoxemia as in mitral disease and mountain sickness, gives rise to such compensatory phenomena as polycythemia, increased size of red blood cells and increased corpuscular and blood volume, one would expect similar changes in emphysema. Reported observation of such compensatory changes are rather conflicting. Some observers report findings within the range of normal, others abnormal. Under any circumstances, the ranges are wide. These discordant results are in part due to different methods employed, but there can be little question that they are largely due to the fact that the time element is missing. Repeated measurements at prolonged intervals in the same individual would be far more illuminating. It is a well attested clinical observation that in longstanding cases of emphysema, marked polycythemia is usually marked and in some cases even an increase in blood volume has been noted (24). Many so-called "black cardiacs" are emphysematics. Arriliga (25) and Escudero (26) have reported a number of such under the false classification of "Ayerza's disease".

3. All observers agree that there is a *retention of* CO_2 in the blood in emphysema. Christie (12) presents evidence which leads him to believe that as a result of the loss of pulmonary elasticity the peripheral distended and relatively ischemic alveoli are overventilated at the expense of the deeper and more normal alveoli. The subsequent diminution of the effective tidal air is held responsible for some if not all, of the anoxemia and CO_2 retention. Scott (27) long before this showed that there was CO_2 retention in emphysema. He also showed that the blood bicarbonate was elevated, thus maintaining the hydrogen ion concen-

tration within normal limits. He also showed that patients with emphysema have an increased tolerance for rebreathing with relatively high percentages (8 to 10 per cent) of CO_2 for 10 to 15 minutes, showing relatively little increase in minute volume and evincing no subjective symptoms of distress. Slightly higher percentages of CO_2 cause acute distress. These observations have been confirmed.

Effect of emphysema on the heart. Although in the past doubt has been expressed in some quarters as to whether emphysema affects the heart, all are now agreed that it does, and that the primary mechanism is hypertension of the pulmonary circulation. There is no clinical method of measuring the pressure in the lesser circulation[2] but the accentuation of the second pulmonic sound in uncomplicated emphysema indicates its presence.

There are a number of possible peripheral resistances that may contribute to the development of hypertension of the pulmonary circuit: a. the diminution of the capillary bed due partly to atrophy of the walls of the alveoli and partly to actual desruction by rupture of many of the alveolar septa. The pale color of emphysematous lungs in the early phases is the expression of these factors. b. the expansion of the alveoli causes a compression and stretching of the interalveolar arterioles (28). c. Fishberg (24) suggests that the chronic cough raises the intraalveolar pressure to such an extent as to compress the minute vessels of the lungs; the hypertrophy of the right heart occasionally observed in pertussis may be accounted for by the same mechanics. d. it is possible that the less negative intrapleural pressure may compress the thin walled pulmonary veins sufficiently to cause a rise in pulmonary arterial pressure.

A sustained rise in intraarterial pulmonary pressure leads inevitably to hypertrophy of the right ventricle. Kirsch (29) found in emphysema that the dilatation and later hypertrophy first affected the outflow tract, a process precisely comparable to that observed in the left ventricle in hypertension of the greater circuit. This was confirmed by Parkinson and Hoyle (30) radiographically and checked by post-mortem observations. They found a prominent conus which in part represents the outflow tract, in 33 of 90 cases of emphysema. In later stages the body of the right ventricle enlarges due to enlargement and dilatation of the inflow tract.

Coincidentally, dilatation of the pulmonary artery occurs. This is apparent during life roentgenologically by the increased width of the pulmonary artery at the hilus and by the enlarged conus. In later stages, when the dilatation becomes extreme, dancing pulsating shadows may be seen. At post-mortem, dilatation of the entire pulmonary tree always accompanies gross arteriosclerosis of the pulmonary vessels, the hall mark of hypertension of the pulmonary circuit.

Clinically enlargement of the right heart in the early stages of emphysema may not be susceptible of proof because the low diaphragm causes the heart not only to drop but to rotate so that the transverse diameter is not appreciably widened.

[2] Recently Cournand has been able to measure the pressure in the right auricle by introducing a catheter by way of the brachial veins. It seems to be a harmless procedure and has already contributed much to our knowledge of the dynamics within the pulmonary circuit.

Pulmonary arteriosclerosis. We have previously expressed the view (10) (see Chapt. 12) that arteriosclerosis is a process that begins at birth, characterized essentially by a progressive splitting and hyperplasia of the elastica and of the intima, and that these changes represent an adaptation to the progressive rise in intravascular pressure that proceeds from birth to maturity. When hypertension occurs, the process comes earlier and is accelerated and intensified. The pulmonary artery also partakes in this process (31) but inasmuch as the pressure within this vessel is low (only one-sixth that in the aorta) the pulmonary artery is singularly free from gross changes of arteriosclerosis as compared to the vessels of the greater circulation. For this reason there is a remarkable difference in incidence of gross arteriosclerosis between the two circulations. When however, hypertension of the pulmonary circuit arises, the normal hyperplastic process is intensified, and gross arteriosclerosis becomes manifest. With the exception of rare instances in senile individuals, gross arteriosclerosis of the pulmonary artery never occurs unless a lesion that might dynamically cause a hypertension of the pulmonary circuit is present (31). Pulmonary arteriosclerosis is therefore, as we previously stated, the hall mark of hypertension within this vessel. We have not observed an emphysema of any degree or duration that did not reveal gross arteriosclerosis of the pulmonary artery. That emphysema is a common cause of pulmonary arteriosclerosis is shown by the fact that in 62 such instances, emphysema was found in 12, a percentage of 19.3 per cent. The hypertension in the pulmonary circuit in emphysema is reflected not only in the arteriosclerosis within the pulmonary artery but also in sclerotic changes in the endocardium. In uncomplicated emphysema the endocardium of the right ventricle and to a lesser extent of the right auricle show thickening. The endocardium of the left side of the heart is intact, in contrast to uncomplicated hypertension of the greater circulation when the endocardium of the left side of the heart shows thickening. Eventually the increased pressure in the pulmonary circuit is reflected forward into the pulmonary capillaries. These dilate giving rise to a beaded appearance of the alveolar wall and the alveolar lumen becomes narrowed, which accounts for some of the loss of vital capacity. The dilatation of the capillaries is always accompanied by a fibrous thickening of the capillary wall which in places becomes hyalinized. One may regard the entire process as an arteriocapillary fibrosis, precisely comparable to that which occurs in the greater circulation in hypertensive disease. Under such circumstances, the emphysematous lung changes its physical characters; it becomes carneous, firm and congested. Some years ago I (32) described such a lung in a patient in whom over a period of many years, I had observed, the transition from pure bronchial asthma to emphysema, and finally to right sided cardiac failure.

It must be insisted upon that the clinical phenomena associated with emphysema are not the direct result of the arteriosclerosis of the pulmonary arteries as some aver, but the result of the altered dynamic forces that evoked it.

The increased amplitude of contraction consequent upon the hypertrophy of the right ventricle compensates for the increased pulmonary resistance for a great or lesser period, often for years. Eventually, unless an intercurrent complication arises, the compensation no longer suffices and dilatation of the in-

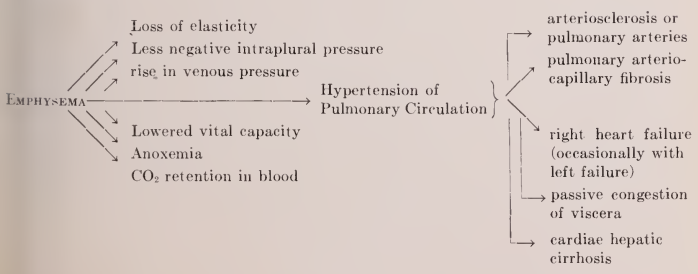
flow tract of the right ventricle ensues. This is evidenced roentgenologically by an an increase in the size of the right ventricle. This dilatation in turn forces the right auricle to empty against a positive pressure and an appreciable rise in venous pressure results. The increased pressure within the right auricle extends downward through the inferior vena cava into the hepatic veins and thence into the liver which enlarges and becomes nutmeg in appearance. This entire system dilates and forms a reservoir which acts temporarily as a dam against the steadily mounting venous pressure. In time cardiac cirrhosis arises which is always associated with sclerosis of the hepatic veins (33). The morphological changes in the liver represent pathogenetically a venocapillary fibrosis, comparable to that which occurs in the lung, the hepatic vein taking the place of the pulmonary artery. These processes within the liver are not peculiar to emphysema but follow any prolonged hypertension of the pulmonary circuit from any cause (see Chapt. 1).

A rise of venous pressure well beyond the normal range is therefore one of the earliest manifestations of beginning failure of the right heart. Death often occurs from pure failure of the right heart with the classical picture of intense cyanosis, breathlessness, low grade renal insufficiency and anasarca. The entire series of events conforms to the typical clinical picture of "cor pulmonale", a common sequence of obstructive emphysema. Of 48 cases of "cor pulmonale" observed by Scott and Garvin (34) 46 were associated with emphysema. In 32, emphysema was the sole cause; in the remainder the emphysema was associated with silicosis or tuberculosis.

Occasionally in emphysema involvement of the left ventricle follows. There are a number of possible explanations. 1. According to Starling and his coworkers (35) a sustained and progressive rise of effective venous pressure causes an increased stroke volume in the left ventricle. This inevitably leads to hypertrophy and eventually to dilatation. 2. The anoxemia must augment the work of the left ventricular muscle that is already overburdened by an increased venous return. Such a heart requires more oxygen than normal but the amount falls short owing to reduction in coronary flow that accompanies dilatation of the heart (36, 37).

More often, left ventricular enlargement in emphysema is the result of an associated hypertension or coronory disease, since these maladies have the same age incidence.

BIOLOGY OF EMPHYSEMA



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MASSIVE PULMONARY EMBOLISM VIII[1]

Based in Part on a Study of Eighty-eight Fatal Cases[2]

HAROLD NEUHOF, M.D., and SAMUEL H. KLEIN, Lt. Col., M.C., A.U.S.[3]

VI. TREATMENT OF MASSIVE PULMONARY EMBOLISM

A. *Medical Treatment.* The reason for discussing pulmonary infarction here lies in its possible relationship to massive pulmonary embolism.

Symptoms of minor severity caused by simple infarctions require, as a rule, only morphine or codeine to alleviate cough, tachypnea and pleuritic pain, and also oxygen, if cyanosis is present. Immobilization of the affected side of the chest by means of adhesive strapping may also be used if pleuritic pain is troublesome. The fact that an infarction has occurred is an indication that a focus of thrombosis is present. In view of the well-known tendency for pulmonary embolism to recur, every effort must be made to prevent a repetition of the accident. The patient should be kept quiet, using sedatives as liberally as necessary to allay nervousness and apprehension. He should be moved as little as possible. It might be wise, in this connection, to forego fastidiousness for several days, changing the bed linen only if and when absolutely necessary. The lower extremities should not be exercised or massaged at this time. In order to minimize dislodging a thrombus, exertion by the patient should be avoided as much as possible.

Emphasis should be placed on the fact that it is in this type of case that division of the femoral vein has been recommended to prevent further and perhaps fatal pulmonary embolization.

Regardless of any other therapy, the first treatment for a patient with pulmonary embolization should be a substantial dose of morphine. For the emergency treatment of massive pulmonary embolism deTakats and his co-workers (2, 75, 118) advocate the administration of a combination of atropine and papaverine. As noted in a foregoing section, their recommendation is based on the results obtained in animal experiments which seem to indicate that autonomic reflexes consisting of vagal impulses originating in the occluded pulmonary arterial tree produce constriction of the smooth musculature of the coronary arteries, the bronchi and the upper gastro-intestinal tract, thus contributing to the cause of death from pulmonary embolism. Atropine is therefore given to inhibit vagal impulses, and papaverine is administered to relax contracted smooth muscle.

[1] This is the eighth installment of a series of articles dealing with the problem of Massive Pulmonary Embolism. Upon completion of their publication they will be collected and reprinted in a single volume, constituting one of the Series of projected Monographs of The Mount Sinai Hospital Press.—Ed.

[2] From the Surgical and Medical Services and the Laboratories of The Mount Sinai Hospital, New York.

[3] Lt. Col. Klein, as adjunct surgeon to The Mount Sinai Hospital, has contributed the study of the fatal cases and the analysis on which the work is based.

Recently, further observations (118) were made on animals which indicate that atropine acts rapidly while the action of papaverine on the smooth muscle of the bronchus comes on much more slowly but may last longer. Therefore, and because of the excellent action of papaverine on the coronary flow, the combination of atropine and papaverine seems preferable to the use of each drug alone. DeTakats and Jesser (2) recommend that the papaverine be given in $\frac{1}{2}$ grain (0.03 Gm.) doses, and the atropine in doses of from $\frac{1}{60}$ to $\frac{1}{75}$ grain (0.001 to 0.008 Gm.). It is advised that both drugs should be given intravenously, as absorption from subcutaneous or intramuscular sites is too slow in patients requiring emergency treatment. The authors' surgical floors are provided with $\frac{1}{2}$ grain powders of papaverine and $\frac{1}{150}$ grain tablets of atropine, and the drugs are dissolved in a few cubic centimeters of physiologic solution of sodium chloride and boiled over a flame just before use. Although papaverine solutions are available in ampules, their stability seems to be variable. Thus, the potency of the drug is probably greatest when solutions are freshly prepared as required.

DeTakats and Jesser compare the survival rate in a series of 22 cases of pulmonary embolism treated with atropine, papaverine, or both, with that in an untreated control group of 100 cases. In the former, 18 cases (82 per cent) survived, while in the control group only 13 (13 per cent) survived. They admit that a comparison of such a small series of patients with a larger series not having received any medication is hardly absolute proof, but maintain that it does reveal a marked drop in mortality when these drugs are used.

In view of the marked pressor effect of epinephrine on the pulmonary vascular bed as observed experimentally following artificial massive pulmonary embolism with marked cor pulmonale and dilatation of the superior and inferior vena cava, the use of this and allied drugs is condemned (119). It has been maintained that even comparatively small doses given when the pulmonary arterial pressure is already abnormally high may lead to pulmonary edema.

In order to counteract the associated vasomotor disturbances which aggravate the mechanical difficulties of the pulmonary circulation produced by pulmonary embolism, Leriche, Fontaine and Friedmann (120) recommend immediate infiltration of the stellate ganglion with one per cent solution of procaine hydrochloride without epinephrine. The choice of the side to be injected is determined by the site of pain, if it is distinct, but if there is no indication of the localization of the embolism, the infiltration should be bilateral.

B. *Surgical Treatment.* In 1908 (121) Trendelenburg reported his classical work, demonstrating experimentally that complete compression of the pulmonary artery could be tolerated for from 45 seconds to 2 minutes, and that partial compression could be successfully withstood for several minutes. At this time, he reported the first two cases of pulmonary embolism operated upon in man. The first lived fifteen hours and died of heart failure; the second died thirty-seven hours postoperatively of hemorrhage from the internal mammary artery.

Since that time the operation of pulmonary embolectomy has been attempted

or completed by a few surgeons. Nygaard (87), in 1938, found that 132 cases had been reported in the literature with a mortality of 93.2 per cent. In table 12 is a list of successfully operated cases culled from the literature by Nystrom (122).

In 1935, Mustman and Hallervorden (123) reported six cases in which the operation of pulmonary embolectomy was performed during the course of two years. Three of these patients survived for a number of hours.

Lewis (124) in 1939 reported another case, the first successful pulmonary embolectomy recorded outside of Continental Europe, and also noted a successful pulmonary embolectomy reported by Valdoni (125) of Rome in 1936.

In following the more recent literature, it is evident that most authors have concerned themselves with almost every phase of the subject except that of operative treatment. Occasionally, embolectomy is mentioned as a possibility

TABLE 12

OPERATION	YEAR	SURVIVED OPERATION
Sievers-Trendelenburg	1908	15 hours
Trendelenburg	1908	37 hours
Kruger	1909	5¼ days
Sauerbruch	1914	50 hours
Kirschner	1924	Discharged, healed
A. W. Meyer	1927	Discharged, healed
Crafoord	1927	Discharged, healed
Nystrom	1927	30 hours
Nystrom	1927	5 hours
Nystrom	1928	Discharged, healed
Crafoord	1928	Discharged, healed
Meyer	1928	Healed; died of new embolus 25 days later
Meyer	1928	Discharged, healed
Nystrom	1929	3 hours
Nystrom	1929	Discharged, healed

under favorable circumstances, without any detailed discussion of what these favorable circumstances might be. In general, the latter have received only scant attention.

There are several reasons for an unfavorable attitude toward pulmonary embolectomy: 1. The high mortality in the attempted cases; 2. A highly trained hospital organization is required so that the operation may be carried out with a minimum of delay; 3. In view of its emergency nature, the operation may frequently have to be performed by junior surgeons or house officers with limited operative experience; 4. The diagnosis is often difficult and not infrequently even impossible; 5. A severe clinical picture may be produced by *peripheral* pulmonary embolism; 6. Patients may recover from apparently fatal pulmonary embolism; 7. It is impossible to determine clinically whether, in any given case, the distribution of the pulmonary emboli is such that successful embolectomy

and restoration of the pulmonary circulation will be feasible. All these reasons, however, do not shut the door on the consideration of embolectomy but limit, rather, the horizon of the operation. An analysis of the 88 consecutive autopsied cases which have been reported in this monograph, provides some precise information on the whole question. That analysis can be set forth briefly at this point as a summary of much that has already been presented in considerable detail in preceding chapters.

Since there has been some question as to the cause of death in cases of massive embolization of the pulmonary artery, it should be stated at the outset that the study of the 88 fatal cases establishes that obstruction of the pulmonary artery usually is the essential cause. The factors producing death were obstruction, asphyxia, and heart failure. The fatal episode took place at virtually any time during a medical illness (26 cases) or in the surgical postoperative period (62 cases). Of the 62 deaths in operative cases 21 occurred in the first week, and of these, 14 in the first few days. Only 26 were encountered in the second week, chiefly in the classical period of the eighth to twelfth day. Some details will be given later concerning the time of death in relationship to the onset of symptoms.

An analysis of the 88 cases reveals that there was evidence at autopsy of previous *peripheral* embolization in 43, that is, in half the cases. 36 of the patients had had symptoms and signs related to such earlier episodes, and in at least 13, there were local manifestations suggesting the presence of thrombosis or phlebitis. If argument were needed, these data would supply a powerful one for thorough going prophylactic measures in any hospital service, medical or surgical.

The variations in the size, shape, and position of the pulmonary embolus were studied and were found to be of surgical significance. Some emboli were extremely long with twig-like branches, others short and curled up. Some were firm, others friable. A few were firmly adherent. The embolus was situated (1) in the outflow tract of the pulmonary artery, (2) in the main trunk, (3) in one or more of the major branches, or (4) fragmented and distributed in the lesser branches. Thus it is obvious that the chances of encountering and removing the embolus at operation cannot be gauged in advance.

The symptoms in the 88 cases were those of asphyxia, shock, syncope, or heart failure, singly or in various combinations. Variations in symptoms and signs often made an absolute diagnosis difficult or impossible except in classical cases. Central and peripheral blockade could not be differentiated. Perhaps the most significant conclusion from the study of symptoms was that there was *no dependable relationship between the degree, location, and extent of the pulmonary embolus, and the clinical picture.* The literature scarcely deals with this aspect of the subject and yet the question must be raised as to when so formidable a procedure as the Trendelenburg operation is indicated.

Although the classical cases can be recognized readily, it can be said that the differential diagnosis from coronary thrombosis in particular or unrelated lesions in general may be difficult or virtually impossible. The electrocardiogram is not of decisive aid in the differentiation from coronary thrombosis. In our 88 cases

an unequivocal diagnosis of pulmonary embolism was made in 16, an equivocal one in 13. The diagnosis was incorrect in 22. The clinical picture in 13 cases did not appear to suggest or at any rate did not warrant a diagnosis of pulmonary embolus.

From a consideration of the topographical features alone, embolectomy would have been feasible in 33 of the 88 cases. However amongst these 33 cases there were no distinctive clinical features to differentiate them from less favorable cases. The conclusion is therefore inevitable than an operation always must be regarded as an exploratory one. Of the 88 cases, almost half were suffering from otherwise irremediable conditions. A survey of all the features of the 88 cases including diagnosis, duration of symptoms, topography of the embolus, etc., establishes that there were between 15 and 26 cases spread over a period of 10 years in which favorable criteria for embolectomy existed.

The occurrence of death after the onset of symptoms was within 10 minutes in 18 cases, in 11 to 15 minutes in 9 cases, in 16 to 30 minutes in 11 cases, and in one half to one hour in 8 cases. Twelve died in one to 4 hours, 6 in 4 to 10 hours, 5 in 10 to 24 hours. Thus a significant fact concerning the cases to be regarded as favorable for embolectomy was that the duration of life was short in many. This is quite out of line with the protracted duration of life for which the Trendelenburg operation has been advocated.[4] In this connection reference should be made to a number of cases studied but not included in our series, characterized by extremely severe clinical manifestations of prolonged duration with recovery ensuing after death was anticipated. Some of these cases would conform to the type in which the Trendelenburg operation might have been performed in accordance with the formula of observation over a period of hours.

The objections to the Trendelenburg operation are: (1) An extremely high mortality; (2) The requirement of a hasty operation because of the short period of permissible occlusion of the pulmonary artery; (3) A too formidable operation in case of error in diagnosis; (4) An unsuccessful operation if the embolus is not of classical topography and in the typical situation; (5) The requirement of a specially trained team; (6) The limitation of operation to a rare clincal variety of pulmonary embolism.

Because of the criticisms of the Trendelenberg operation which have been raised, an operative procedure was devised which met some of the objections to the classical procedure. The technique of the Trendelenburg operation has not been detailed here but it will be recalled that the essential (and most objectionable) feature of the procedure is a clamp which shuts off the pulmonary artery in order to permit incision and extraction of the thrombus. The operation devised, and which has already been reported (129), rests on the principle of non-interference with the pulmonary artery, the attempt being made to extract the thrombus by suction through an incision in the right ventricle. The case in which the operation was performed will be described briefly and the

[4] The classical indication for operation is a slow deterioration over a period of hours, operation being decided upon when death obviously is impending.

absence of the thrombus in the main trunk of the pulmonary artery should be noted. A brief comment will follow the description of the operation.

ILLUSTRATIVE CASE

History. E. P. (Adm. # 498441), an 18 year old athlete, had been well until 16 days before admission. There then began a left lower lobe pneumonia with treatment by sulfathiazole and subsidence in a few days. Four days before admission there was an episode of pain in the right lower chest and shoulder, and fever, with subsidence. The evening prior to admission there was an attack of left chest pain. Three hours before admission there was a sudden access of left anterior thoracic pain, a chill, and severe dyspnea. His physician found signs of vasomotor collapse with a rapid thready pulse, cold and cyanosed extremities; blood pressure was not obtainable.

This was the condition on admission at 10 a.m. By 11:30 a.m. there was some improvement apparently as the result of the administration of oxygen and morphine. A systolic blood pressure of 85 was obtainable by auscultation. An electrocardiogram revealed changes which were compatible with acute cor pulmonale or pulmonary embolus. The chest film disclosed no definite abnormality in the lungs. Papaverine was administered intravenously and heparin shortly thereafter. The improvement which had set in proved to be transient. By 4 p.m. the pulse was imperceptible at times, the systolic pressure 70, the patient semi-comatose. At 4:50 p.m. the patient was comatose and the general condition poor. There was slight improvement thereafter apparently the result of a transfusion of blood. There were periods of partial consciousness but the pulse and blood pressure became scarcely obtainable, the heart sounds faint, and the vasomotor collapse extreme. At the time of operation, 8:45 p.m. the patient was not responsive and death appeared imminent.

Local anesthesia was employed but there appeared to be little need for any form of anesthesia. A right parasternal incision was made through the fourth and fifth costal cartilages and the adjacent portion of the sternum was removed with rongeurs. A substantial proportion of the pericardium was exposed extrapleurally and was incised. The right auricle and ventricle which were pulsating with little force were well visualized. By palpation the pulmonary artery appeared empty of thrombus but of this one could not be sure. Two parallel silk sutures were placed through the most prominent portion of the right ventricle and an incision through the wall of the ventricle was made between them. The escape of blood was stopped effectively by the introduction of an open end No. 34 French catheter (child-sized rectal tube) and the crossing of the sutures over the catheter (a metal tube would be more effective for the purpose). The catheter was passed upwards the short distance necessary to bring it to the outflow tract of the pulmonary artery and suction was applied. The blood was drawn and filtered into a flask containing citrate solution with the intention of returning the citrated blood to the circulation. When thrombotic material was not observed in the gauze filter the catheter was withdrawn from the ventricle and saline solution drawn through the system in order to see if a thrombus had been extracted. The crossing of the two sutures after the withdrawal of the catheter prevented escape of blood from the ventricle. The catheter was then introduced and removed a second time and again no thrombotic material was withdrawn. The maneuver was again repeated, the catheter being passed into the pulmonary artery this time. No thrombotic material was obtained, the catheter was withdrawn, the sutures were tied across the incision in the ventricle, and one additional suture was passed and tied in order to stop some leakage of blood. The duration of operation to this point was one half hour. Death occurred fifteen minutes later.

The autopsy disclosed an empty main trunk of the pulmonary artery. Thrombi filled the right and left branches beginning in each instance 2 to 3 cm. from the main trunk. They extended into the smaller branches of both sides. They were friable and, micro-

scopically, revealed beginning organization. The lungs showed infarcts on both sides. The incision in the heart was found to be about 2 cm. in length and was situated in the anterior aspect of the right ventricle.

Comment. The operative procedure is simple, reasonably safe, and does not require undue haste. Special skill and practice and a special team are not needed. The suction results in some measure of decompression of a right ventricle which is laboring unavailingly against the obstructing embolus and thus is a desirable feature. However, the essential part of the operation is performed blindly and does not provide assurance that suction will in fact engage the thrombus in the eye of the catheter or the end of a metal tube. Despite the hazardous nature of the procedure, further attempts to extract the pulmonary embolus through the embolus through the right ventricle appear justified. It may be added, on theoretical grounds, that a milking backwards towards the ventricle of a thrombus which can be felt in the pulmonary artery would aid in its extraction by suction.

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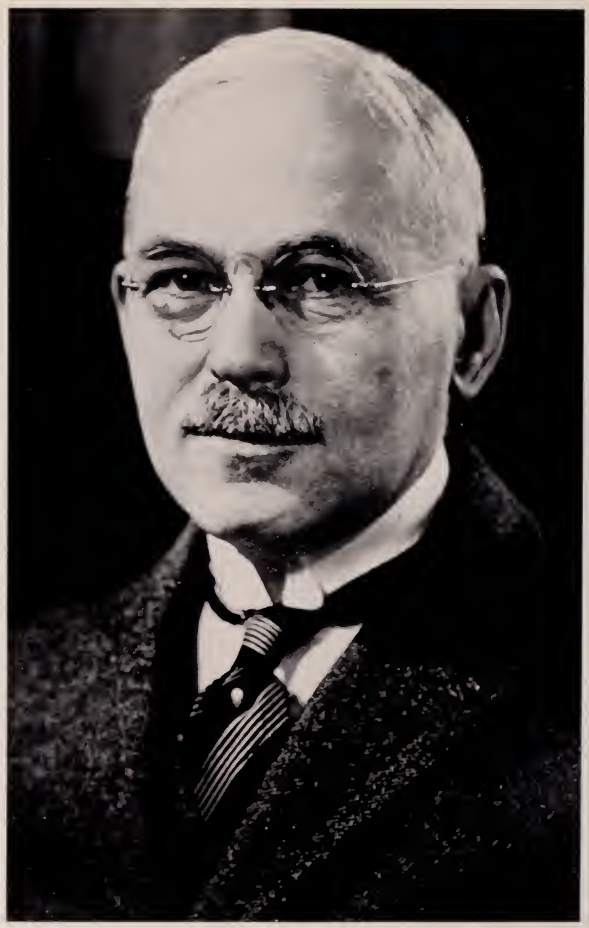

Howard Lilienthal, M.D.

Howard Lilienthal, M. D.

January 9, 1861—April 30, 1946

A mere reading of the more than three hundred titles listed in the Bibliography of Dr. Howard Lilienthal shows his wide diversity of interests. If to that reading there is brought even a meagre knowledge of the history of surgery then one recognizes the boldness, the pioneer spirit and the achievements of the author. Professional attainments represent only one side of the man, and are better appreciated when the man himself is known.

Howard Lilienthal was born on January 9, 1861, in Albany, New York. His father, Meyer Lilienthal, and his mother, Jennie Marcus, had both been born in Germany. From his father, who was a taxidermist by avocation, he was stimulated to learn and love nature. He was the eldest of five children. He received his early education in the Albany Boys' Academy. The family then moved to Saratoga Springs where he attended Saratoga High School, graduating in 1887. During the next two years he studied under a private tutor. He entered Harvard College in 1879 where four years later he graduated cum laude. In college his extra-curricular interests were wrestling and singing. He had a fine tenor voice. By his choir work Howard Lilienthal helped defray his college expenses. Upon graduation from college he began his medical studies at the Harvard Medical School and received his M.D. degree in 1887 after three years at that school, and the fourth year as interne at McLean Asylum, then located at Somerville, Massachusetts. In the house staff examinations for internship at the Mount Sinai Hospital of New York he made first place and chose the surgical service. Thus began an association which lasted nearly sixty years.

We may leave for the time being the young surgeon starting on his career to look at the young man.

In 1891 he married Mary Harriss d'Antignac of Savannah, Georgia. She died in 1910. Of the union there were two children. The daughter, Mary d'Antignac Lilienthal, married a West Point graduate, Thompson Lawrence, now a Major General in the United States Army. The son, Howard Lilienthal, Jr., was a student at Harvard at the outbreak of World War I. He went overseas with the 107th Infantry regiment of the Twenty-Seventh Division and was killed in action on September 29, 1918. In 1911 Dr. Lilienthal married Edith Strode of Amherst, Virginia. Her charm, sympathetic understanding, and devotion were of immeasurable help and inspiration to him through the years.

On completing his service as house surgeon at the Mount Sinai Hospital Dr. Lilienthal entered private practice. His first office was at 43 East 29th Street. Shortly thereafter he became an assistant to Dr. Arpad Gerster, one of the outstanding surgeons of that day, under whom Dr. Lilienthal served while in the hospital. He continued as part-time assistant for eight years of delightful association. Much of the operative work at that time was done in the patient's home, whether it was tenement or mansion. This led Dr. Lilienthal to devise a portable operating table in 1902. It was a metal table which folded into a case

8 inches wide and 21½ inches in the other dimensions. With this table, which was firm when opened, many positions desirable in operating could be obtained.

At the Mount Sinai Hospital Dr. Lilienthal rose through the ranks to the rank of an attending surgeon in 1899, holding that position until he became consulting surgeon in 1922. For many years he was also attending surgeon at Bellevue Hospital, and was associated in consulting capacity with the New York Infirmary for Women and Children and the Hospital for Joint Diseases.

To serve for twenty-three years as the head of an active growing surgical service means much if heading that service means what it says. Dr. Lilienthal really headed his service: he led, guided, and stimulated. New and progressive ideas came more frequently from the top of the service. He too grew with his service until the time he left it.

Dr. Lilienthal's successful leadership is attested to by his election to the presidency of many medical and lay societies. He became a member of the Harvard Club in 1887. A charter member of the Harvard Medical Society of New York, he served as its president in 1901. In 1915 he served as president of the Medical Society of the County of New York. He was one of the founders of the American Society for the Control of Cancer (now American Cancer Society). In 1891 he was elected a fellow of the New York Academy of Medicine. He was a senior member of the American Surgical Society and the New York Surgical Society. He served as president of the latter organization. He was president of the New York Society for Thoracic Surgery and held a like position in the American Society for Thoracic Surgery. He was a member Correspondent of the Societe Internationale de Chirurgie de Paris. He was a charter member of the New York Chapter of the Military Order of the World Wars and served as its surgeon general. He was past commander of the Caduceus Post 818 of the American Legion, and president of the New York Physicians Art Club.

Some have forgotten and many do not know that "Reserve Officers", a term so commonplace today, originated well before World War I for the medical profession. To be exact, the medical reserve corps was begun in 1908. Dr. Lilienthal joined this in 1911, and was commissioned a first lieutenant, the only rank then granted. When World War I began in Europe, Base Hospital Units were formed in the United States under the auspices of the American Red Cross and Base Hospital #3, the Mount Sinai Unit, was organized. When it was mobilized Dr. Lilienthal was made its director with the rank of Major. He was then 57 years old. The Unit crossed the Atlantic in February, 1918 at a time when the submarine menace was real. No one who sailed with him will forget the trip nor his cheering influence. He circulated constantly from one group to another. He sat and talked with some of the older nurses; he joined another group in singing with the same clear melodious voice that the Harvard Glee Club had known back in 1880; he played chess with some, and cards with others.

Shortly after arriving in France Dr. Lilienthal was advanced to the rank of Lieutenant Colonel. He subsequently was allowed to decline promotion to the rank of Colonel, a rank he feared would interfere with active operative work.

His work, however, was not confined to Base Hospital #3, but as director of a surgical team, he did thoracic surgery in Evacuation Hospital #8 and United States Army Hospital #101. He was cited for the D. S. M.

Dr. Lilienthal was one of those fortunate individuals who knew how to play as well as how to work. He was a great lover of the outdoors and outdoor sports. He enjoyed tennis and played long after many of his friends thought he should have given up. When he finally abandoned tennis he substituted hunting or walking through the woods accompanied by his dog. Of several dogs in his life, Duke, a spaniel, was probably the best loved. He was a good bird dog, yet perfectly at home in the living room where, as he grew older, he would occupy, unadmonished, one of the chairs. He was trained by Dr. Lilienthal not only as a bird dog but to do many tricks. He was often photographed and painted by his master. Dr. Lilienthal was an ardent dry fly fisherman. He used barbless hooks so that he could throw back into the water, without injuring them, those fish he did not wish to keep. A story is told of an army officer fishing in the far West who astonished his guide by using barbless hooks. The guide stated that only once, many years previously, had he seen a fisherman use such hooks, a doctor from the East. When asked by the army officer if he remembered if his name was Dr. Lilienthal, the guide said it was. The officer then replied, "He is my father-in-law."

Dr. Lilienthal was interested in the graphic arts. He worked in oils, water colors and pastels. He showed ability and exhibited at the annual exhibition of the New York Physicians Art Club. A pastel, "Corner in the Library", was voted the best pastel in the 1934 exhibit. Of recent years some difficulty with his vision prevented him from continuing his painting. Then he turned to short story writing and had published several short stories for children.

Reference to Dr. Lilienthal's bibliography shows how diversified were his contributions to general surgery and how his interests gradually centered on his chosen field of thoracic surgery although not to the exclusion of other topics.

His earliest published paper was in 1892 four years after he entered practice. It dealt with suturing of tendons and nerves at the wrist. From that time on, each year that he was in "active" practice saw articles published. There are described seven instruments or kinds of equipment which he devised. The first was in 1896, a bullet probe and bullet forceps; in 1902 came the operating table previously mentioned; in 1906 a self-retaining trocar and cannula for aseptic evacuation of distended viscera; in 1925 he described a rib spreader and a guillotine type of rib cutter. These represent only the instruments which he put on record. There were many improvisations made to meet special problems as they arose. One example may be given. He found that using a small flashlight bulb on the end of a stomach tube through which the wires passed to a battery, he could, when this tube was passed and lighted, more promptly identify the esophagus in the posterior mediastinum.

If his reports are viewed from a regional standpoint we note contributions made to the treatment of fractures and infections of the extremities. Among these is a report in 1896 of an osteoplastic operation for the loss of substance of

the tibia with a skiagraph showing the end result. This is one of the earliest demonstrations of the application of x-ray. In the same year Dr. Lilienthal had employed x-rays in the diagnosis of a tumor of the superior maxilla in which the plate was placed inside the mouth just as the films are used today, but which at that time showed real imagination. Other writings deal with operative procedures carried out on the head, face, and neck. Among them he described, in 1911, an original approach to the tempero maxillary fossa for dealing with affections of that joint. Its merit lies in the adequate exposure gained and safeguarding of the facial nerve.

In the field of Genito-urinary surgery Dr. Lilienthal was an ardent advocate of suprapubic prostatectomy. In 1902 he reported his results in seven cases. His paper published in 1905 was based on thirty-one cases. Two of these were two-stage operations. In 1906 he published a letter in Medical Record in which he pointed out his priority in doing a planned two-stage suprapubic prostatectomy. In 1911 he described a surgical approach for performing a complete nephro-ureterectomy which followed the general pattern of his procedures in being simple, practical and a respector of the human tissues.

At the turn of the century Dr. Lilienthal wrote many papers on the treatment of diseases of the biliary system. He performed his first cholecystectomy in 1896 and was one of the early advocates of primary cholecystectomy in suitable cases. Thanks to present day diagnostic methods the patient with disease of the biliary system is referred to the surgeon at a much earlier stage than was the case thirty years ago. At that time the patient was, in many instances, a very sick individual. However, this did not apply to all of them. One of the less sick ones who in addition was slender was being operated upon by Dr. Lilienthal. The procedure appeared so simple that his assistant, the house surgeon, remarked upon it. Dr. Lilienthal responded that he supposed the house surgeon would like to do a cholecystectomy and was assured he would. "Very well", said Dr. Lilienthal, "You shall do the next one." But the next patient admitted was obese, jaundiced, and very sick. Just prior to the operation Dr. Lilienthal mindful of his promise but also mindful of the best interests of the sick woman said to the house surgeon, "This is the operation I promised you, but the patient is very sick. You let me do it and you shall have the next two cases." He kept his promise.

A reference to the bibliography shows that beginning with about 1914 Dr. Lilienthal's writings dealt almost exclusively with problems of thoracic surgery. He had made valuable contributions to abdominal and genito-urinary surgery but here was a new challenge. What could surgery contribute to the relief of pulmonary tuberculosis, lung suppuration and carcinoma of the lung and esophagus. He met this challenge by thoughtful, well-directed efforts. Today there are improved diagnostic methods, refinements in technique and better means of combatting shock. In the early days fortitude was required to go on in the face of many disappointments.

He did his first lobectomy for chronic suppuration on February 17, 1914. The

child recovered. In 1921 he reported on 31 cases in which lung excisions were done or intended. The mortality rate was high, but the successful cases demonstrated the validity of the procedure. In the same year he reported the successful resection of the esophagus for carcinoma through a posterior mediastinal approach.

In 1925 he published a two volume work on Thoracic Surgery. It was the first treatise in English on the subject. It is based on the personal experience of the author with the various topics he discusses. Evarts A. Graham writing in 1941 says of it, "Thoracic Surgery published nearly twenty years ago is still a classic."

This brief sketch has high lighted some of the accomplishments of Dr. Lilienthal. It has shown how he worked and how he played. From it we realize that he was an outstanding surgeon, a pioneer in surgery, a chosen leader in the organizations to which he belonged, an artist and a sportsman. Yet he could be all this and still not be the man we knew—this man who can best be epitomized as a warm-blooded, sympathetic, enthusiastic and very human fellow man. Photographs of him both early and late show a fine looking man with a natural dignity far removed from austerity. His expression is a kindly one which at the same time inspires confidence. In his active days his carriage was erect; he moved quickly. From those who worked with him he expected the same honest and conscientious efforts that he himself gave. He was enthusiastic and forceful in furthering and promoting a cause, a method or an idea in which he believed.

Let us follow him on a hypothetical yet typical day. He appeared at the hospital for rounds promptly when expected. His house officers were ready with all ascertainable data on any new patient. These patients were encouraged by a kindly word from him. To the house staff on rounds, reasons were given for a change in treatment or for conclusions reached in making a diagnosis. When he came to the Children's Ward there was always time to stop and draw pictures for any child well enough to appreciate them. In the afternoon in the operating room no matter how difficult the problem there would be an absence of tenseness. During the operations Dr. Lilienthal carried on constant conversation. If there were difficulties the frequent profane expletives were directed toward the gall bladder, or lung, or tissue of the unconscious patient, and not at the assistants. That night, if attending a medical meeting, Dr. Lilienthal took an active part in the discussions, always contributing some worthwhile thought. After the meeting, no matter how late, a return trip was made to the hospital if there were patients, private or ward, whom he thought he should see.

He had the happy faculty of putting people at ease. A young man in his early twenties after speaking with him for the first time remarked, "He is wonderful. We talked together as though we were the same age." To his patients Dr. Lilienthal was the one person whose advice must be had on any serious question, medical or otherwise, on down through the years. Nor was this feeling limited to his patients. Medical students, internes and residents turned to him years

after their student days. For each there was a sympathetic ear, sound advice and often help. To his colleagues he was a loyal friend.

In the Fall of 1945 his health began to fail. Nevertheless, he made the long trip to Winter Park, Florida, hoping to regain his strength in the friendly climate amid the many good friends of previous winters. It was not to be. He returned North the end of April and died a few days later.

To very few is given the ability to leave the deep imprint that Howard Lilienthal did on the pages of medical progress and in the hearts of his fellow men.

Ira Cohen, M.D.

ABSTRACTS

Authors' Abstracts of Papers Published Elsewhere by Members of the Mount Sinai Hospital Staff

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

Acute Retroperitoneal Abscess and Phlegmon. H. Neuhof and E. E. Arnheim. Ann. Surg., 119: 5, 741, May, 1944.

A study of acute retroperitoneal infections has been based on an analysis of 65 cases. These infections have been classified as abscesses occurring in the lumbar or iliac regions and phlegmonous inflammations diffusely spread in the retroperitoneal tissues. There were 25 lumbar abscesses, 23 iliac abscesses, and 17 diffuse infections. Acute retroperitoneal infections are always secondary. The infection is derived by direct extension from suppuration in an adjoining organ, by lymphatics, and by metastasis from distant foci of infection. The etiology was not determined in one-third of the abscesses, whereas the source of diffuse infections could almost always be stated. Trauma appeared to play a definite rôle in causation in 15 per cent of the abscesses. The most common source of diffuse infections was acute appendicitis (35 per cent). There is a marked contrast between the pathologic features of abscess and phlegmon of the retroperitoneal tissues. The former is well-localized, and the latter is represented by fibrinopurulent or necrotic exudate and small collections of pus, with a tendency to spread beyond the confines of the retroperitoneum. The bacteriology varied with the source of infection, the *Staphylococcus aureus*, *Streptococcus hemolyticus*, and *B. coli* predominating in the abscesses, and the *B. coli* alone or in combination, in the diffuse infections. Iliac abscesses occur more frequently in childhood—61 per cent of the cases in this study. A history of pain and fever was common to all patients with retroperitoneal abscesses. Pain in the lower extremity was noted in about one-half of the cases of iliac abscess, particularly abscess involving the psoas muscle. The symptoms in the diffuse infections were masked by those of the underlying disease, and in only one-fourth of the cases did symptoms suggest a retroperitoneal infection. Tenderness in, and spasm of, musculature in the region of abscesses was a common feature, associated with a mass in 65 per cent of the cases. Abdominal examination revealed a mass in one-half of the cases of lumbar abscess. Psoas (hip) spasm was noted in one-half of the cases of iliac abscess. A suppurative lesion was usually suspected, but the slow evolution of a mass often delayed the diagnosis of retroperitoneal abscess. Operation was sometimes withheld until a mass became evident; some of these lesions were found to be in an advanced state of suppuration at operation. Examination under anesthesia is suggested in cases in which muscle spasticity exists and interferes with the palpation of a mass. There were two general features suggestive of diffuse retroperitoneal infections, toxicity and abdominal distention. The diagnosis of retroperitoneal infection was not made in 65 per cent of the cases of diffuse infection, and in the cases in which the diagnosis was made the extent of infection usually was not realized. The operative approach was extraperitoneal in 83 per cent of the abscesses, and in the cases in which the peritoneal cavity was traversed the diagnosis of a retroperitoneal abscess had not been made before operation. A careful operative technic will avoid peritoneal contamination should the abscess be encountered inadvertently, or, when the lesion is found to be extraperitoneal before pus is encountered, by a new incision for its extraperitoneal approach. The need of full operative visualization and adequate drainage is emphasized and the details of operative technic are discussed. There was a wide difference in the operative mortality of abscesses and diffuse infections—8 per cent in abscess and 100 per cent in diffuse infection. The primary cause of death in diffuse infections was the extent of infection which precluded adequate drainage.

Dermatitis from Cutting Oils, Solvents and Di-Electrics Including Chloracne. S. M. Peck. J. A. M. A., 125: 190, May, 1944.

Dermatitis from cutting oils, solvents and di-electrics is discussed in detail. The pathogenesis of these conditions is described. Dermatitis from cutting oils is probably the most frequent occupational dermatosis. Dermatitis from solvents is probably next in frequency of occurrence. The rôle of soluble and insoluble cutting oils as causes of dermatitis are discussed in some detail. The various solvents found in industry are tabulated and the type of dermatitis they produce are discussed. The action of chlorinated hydrocarbons on the skin are given and the types of the chlorinated hydrocarbons met with in industry are discussed as well as the types of skin eruptions they produce. The methods of treatment and prevention of dermatitis from all of these chemicals are given in detail.

Some General Observations on Cardiospasm. A. Winkelstein. M. Clin. North America, New York, p. 589, May, 1944.

In the experience of the author, cardiospasm is, in most cases a psychomatic disease. Organic disease of the vagus nerve and reflex causes are also of etiologic significance. It is not a spasm but an achalasia (failure actively to open). The dilatation persists despite clinical improvement. Elongation, esophagitis and diverticula may develop. Esophagoscopy is imperative to exclude neoplasm and peptic esophagitis. Psychotherapy and the soft mercury-weighted rubber esophageal bougie are the two best forms of therapy for the patients with a straight, dilated esophagus. For patients with an elongated, figure-of-S esophagus, esophagogastrostomy is indicated. Artificial hyperpyrexia, according to the studies of the author and William Bierman, relaxes the cardia and deserves further study as a therapeutic agent.

Benign Diseases of the Small Intestine. B. B. Crohn. Gastroenterology, 2: 6, 385, June, 1944.

In recent years, additions have been made to the number of diseases affecting the small bowel, and now there must be some subtractions. Primary intestinal tuberculosis, once diagnosed often and with alacrity, is now recognized as a rare occurrence. The vast hygienic improvements in the rural milk control as instituted by the State authorities has practically eliminated bovine herd tuberculosis. This is probably responsible for the human intestinal tract. The diagnosis of intestinal tuberculosis was a broad cover under which many granulomatous and even neoplastic diseases hid their identities. As time passes the diagnosis of gastrogenous diarrhea due to achylia gastrica becomes less and less frequent. Most patients with achylia are actually constipated, and those who are not, usually have another cause for their diarrhea. The tempo of the advance of our knowledge of benign diseases of the small intestine has of late been fast. Out of confusion has come light, and with light have come newer and eminently successful types of therapeutic attack. For in the small intestine the reward of accurate diagnosis is most frequently the relief of the suffering individual and the professional satisfaction of a job well done.

Psychic Deafness in Children. E. Froeschels. Arch. Neurol. & Psychiat., 51: 544, June, 1944.

"Psychic deafness in children" seems to indicate that there are youngsters in whom a trait, and only that trait, is responsible for their lack of any response to acoustic stimuli. But any identification of the pathologic process in the condition under discussion here with the lesion concerned in "hysterical deafness" is wrong, at least in general. The audiometric test is not appliable to children under 5 years of age, and extreme hardness of hearing frequently seems to prevent even older children from giving reliable responses. The writer recommended the method of "direct tone introduction". For this purpose, one end of a rubber tube is inserted by means of an ear olive into the meatus, while the other end touches the whistle (set of 42 whistles comprehending 6 octaves) from which the tone escapes. Experience has proved that if the patient hears the tone, some kind of reflex will result. It seems worth mentioning that the writer has seen only 12 psychically deaf children, although

his experience with patients with speech and voice disturbances covers 60,000 cases. The 3 patients whose cases have been reported, although differing in their responses to the treatment seemed to have in common an initial deafness, and they gained ability to hear by psychologic treatment and by hearing exercises. The same results could be reached by the same method in the other 9 patients. Any explanation of the cause or causes of the clinical picture will necessarily be hypothetic. "Psychic deafness in children" may be explained hypothetically as a consequence of a slight defect in Heschl's convolution. But if a center is not normally adjusted, much that is asked of the child will be more than he can do; this leads to a feeling of uneasiness. This feeling might appear as resistance, opposition and still greater isolation than that caused by the missing function of the center in question. The name "psychic deafness in children" should be replaced by that of "central deafness", as it signifies better the underlying condition.

Coronary Occlusion, Coronary Insufficiency, and Angina Pectoris. A. M. Master, H. L. Jaffe, S. Dack, and A. Grishman. Am. Heart J., 27: 6, 803, June, 1944.

The clinical, electrocardiographic and post-mortem observations have been evaluated in 100 consecutive cases in which the diagnosis of coronary occlusion had been entertained clinically. In 49 cases the ECG pattern was regarded as characteristic of coronary occlusion and this was found post-mortem in 47 of the series. Not every attack of coronary occlusion resulted in a typical ECG, particularly in multiple fatal attacks and in the presence of bundle-branch block. Acute coronary disease should be divided into coronary occlusion and coronary insufficiency. Acute coronary insufficiency refers to focal myocardial infarction or necrosis in the absence of acute coronary occlusion and is precipitated by some factor which increases the work of the heart or reduces coronary blood flow. The ECG pattern is characteristic, presenting RS-T depression and abnormal T-waves in two or more leads, readily differentiating it from coronary occlusion, which produces RS-T elevations and deep Q waves. When the characteristic pattern of coronary occlusion occurs, occlusion will be found at autopsy in 95% of the cases.

Fungus Allergy and Industrial Dermatitis. S. M. Peck. J. Indiana State Med. Assoc., 37: 304, June, 1944.

The relation of fungus infections to the development of industrial dermatitis in industry is discussed. Various manifestations of fungi, both those due to primary fungus infections and those due to allergic reactions to the fungi and their products are described. The differential diagnosis of contact dermatitis of the hands and dermophytids are given.

Inhibitory Effect of Sulfonamides on the Action of Nicotine in the Isolated Intestine. E. P. Pick, G. W. Brooks and K. Unna. J. Pharmacol. & Exper. Therap., 81: 2, 133, June, 1944.

Sulfonamides inhibit the effect of nicotine on the isolated intestine of rabbits and guinea pigs. Sodium sulfathiazole, sodium sulfamerazine and sulfanilamide are more effective in inhibiting the action of nicotine than sodium sulfadiazine. Para aminobenzoic acid fails to antagonize the effect of sulfonamides upon the action of nicotine. The effect of adrenalin, acetylcholine, lentin, prostigmine, histamine, and barium chloride on the isolated intestine is not influenced by sulfonamides. Sulfathiazole does not influence the toxic manifestations of nicotine in frogs, nor does it inhibit the action of nicotine upon the striated muscle of the frog.

A Preliminary Report on Penicillin in Dentistry. L. Stern. Ann. Dent., 3: 1, June, 1944.

The place of penicillin in the treatment of dental lesions remains to be evaluated. Its low toxicity and its selective effect against the organisms commonly recovered from dental infections suggests a wide field of usefulness. Success following local application probably will not be attained until the problem of controlling its solubility is solved. In a series of patients with fusospirochetal gingivitis, 50 per cent definitely improved after 4 days of topical application every 3 hours of penicillin in a cream base, 250 units per gm. Treat-

ment of putrescent root-canals yielded equivocal results. One case of severe submaxillary cellulitis following dental extraction, with a staph. aureos bacteremia, improved remarkably after 3 days of intramuscular injections of penicillin, 10,000 units every 4 hours.

Actinomycosis of the Heart Simulating Rheumatic Fever. A. Cornell and H. B. Shookhoff. Arch. Int. Med., 74: 11, July, 1944.

Actinomycosis is the most common visceral mycotic infection in man, but involvement of the heart in actinomycosis is rare.

Analysis of 3 new cases and of 65 others collected from the literature shows that the heart may be involved by direct extension of the infection from a neighboring organ (most commonly the lungs) or by metastasis through the blood.

Metastatic involvement rarely produces clinical signs. Of the patients in whom involvement of the heart is by direct extension, about half show clinical manifestations.

The most common clinical manifestation in cardiac actinomycosis is congestive heart failure. A pericardial rub was heard in 3 cases and cardiac murmurs in only 2.

The diagnosis of cardiac actinomycosis is rarely made clinically, but it should be considered in every instance of pulmonary actinomycosis, especially since surgical relief of pericardial effusion may be indicated. Cardiac manifestations as the presenting symptoms of actinomycotic infection are rare. Such a picture has been described only once prior to the present report.

The possible routes by which actinomycetes may gain entry to the thoracic cavity are (1) aspiration of the organism into the lungs, (2) extension of a cervical infection, (3) extension of an abdominal infection and (4) metastasis in the blood It is important to recognize that actinomycotic infection may gain access to the thorax by way of the esophagus. In such circumstances extension to the heart is likely to occur.

Obviously the diagnosis of actinomycosis of the heart will be missed in many instances. It should be remembered, however, that cardiac involvement is usually secondary to actinomycosis of the lungs, and the possibility of its occurrence as a complication in the latter disease should be kept in mind. This problem is of more than academic importance. Thoracic actinomycosis is not uniformly fatal. With the help of surgery, radiotherapy and sulfonamide drugs, and recently of penicillin, recovery has occurred in a considerable number of instances.

Nocturnal Secretion Studies in Normals and in Patients with Peptic Ulcer. A. Cornell, A. Winkelstein and F. Hollander. Bull. New York Acad. Med., p. 413, July 1944.

Nocturnal gastric secretion was studied in nine normal males. The older age group was eliminated so as not to introduce an achlorhydria due to age alone. A group of patients with peptic ulcer were also studied. Sixteen test meals were carried out on 14 patients with uncomplicated duodenal ulcer, proved by x-ray or operation. The normal subjects show little or no free hydrochloric acid and specimens were difficult to obtain in most instances because of the small amount of night secretion. Patients with duodenal ulcer secrete a large amount of highly acid secretion during the night. This confirms previous studies in this hospital in 169 cases.

The Absolute and the Unconscious—Freud and America. W. G. Eliasberg. J. of Nerv. & Ment. Dis., 100: 1, July, 1944.

The American absolute is shown to be more than naive boasting about material things. It consists of belief, and as such, causes men rather to die for it than to live with the foreign absolute. Such values as men are ready to die for are the absolutes of a generation. Freud and psychoanalysts after him have tried to substitute the unconscious for the absolute and this has led to misunderstandings of the American scene. The unconscious is repulsive to an unfamiliar absolute. But the generous hospitality the United States has given to psychoanalysis shows that the absolute may act genially, freely, and at times even carelessly towards the unknown unconscious. Culture makes men free and responsive while freedom is denied to the primitive man and to the genius.

Putting Teeth into the Workmen's Compensation Law. W. G. Eliasberg. Medical Record, July, 1944.

Experts' questions have become increasingly urgent in the administration of the compensation laws as generally in the administration of justice. Differences in the experts' opinions may be accounted for by differences in viewpoint (orientation upon the single case or upon statistics), too close cooperation with the parties, too little and too late interest of the compensation board in close supervision, basing opinion on inadequate grounds and couching it in language not understandable to the court and jurors, insufficient training for the particular task of rendering opinions in traumatic disease and traumatic neuroses.

Train Employees to Reduce Needless Waste. M. S. Frank. Hospitals, p. 69, July, 1944.

Despite the best efforts of hospital personnel to conserve all supplies, certain residual end products of the hospital's physical operation always remain. This paper is concerned with the conservation of such waste materials into a source of income for the hospital, which can be gainfully used for patient care, research or education. Over a five-year period, the income from the sale of such waste materials in a large hospital amounted to the surprising sum of almost $17,000. Grease, fat and bones, garbage and swill, used x-ray films, scrap paper, metal, rubber, barrels, tin cans, etc. represent a potential source of income in a well managed institution which should not be overlooked.

Infected Dissecting Aneurysm of the Iliac Artery Following Arteriovenous Fistula of the Femoral Vessels. H. Neuhof. Ann. Surg., 120: 41, July, 1944.

Severe grades of dilatation of the proximal artery in cases of arteriovenous aneurysm of the popliteal or femoral vessels should be treated by excision of the dilated artery. In the presence of infection within the ectatic artery excision is imperative.

The Nature of Psychogenic Cure. C. P. Oberndorf. Am. J. Psychiat., 101: 1, 91, July, 1944.

The article reviews briefly the advance in treatment by psychic means from the supplications of primitive people, Mesmerism, modern hypnosis, Christian Science, etc. to psychoanalysis. After discussion of the question of the interpersonal relationship between physician and patient (transference manifestations), the author discusses suggestion. He defines suggestion as influence on a person through and by means of the transference manifestations of which he is capable. The timing of such suggestions is particularly important. Psychoanalysis operates in the sequential breaking of tensions and the timing of interpretations and explanations at moments fitting for their receptivity. In this sense psychoanalysis becomes an intentional procession of a planned series of psychic situations, each of which in turn becomes favorable for suggestion intended to alter fixed psychic tension. Psychoanalytic thinking has enabled us to reintegrate intra-psychic disharmonies and has brought within the range of a scientifically planned psychotherapy many conditions which previously had never been accessible to any therapy.

Prevention of Epidemics of Dermatitis in Industry Including Dermatophytosis. S. M. Peck. J. Michigan State Med. Soc., July, 1944.

Nearly all of the cases of industrial dermatitis are due to chemical agents. Physical agents and bacteria including the higher fungi play a minor rôle. In order to prevent or control an outbreak of industrial dermatitis it is necessary to have a sound knowledge of (1) the industrial process, i.e., the worker's industrial environment; (2) the chemicals encountered by the worker which are capable of producing a dermatitis; and (3) the mechanism by which these chemicals produce the dermatitis. With these facts thoroughly understood, logical methods for prevention, control and treatment can be instituted. The following topics are discussed at length: patch test, preplacement examination, proper hygienic working environment, protective clothing, cleanliness, and protective ointments.

Inhibition of Nervous Transmission in Synapses and End Plates by Thiamine. K. Unna and E. P. Pick. J. Pharmacol. & Exper. Therap., 81: 3, 294, July, 1944.

Thiamine (5–15 mgm. per 100 cc.) inhibits the action of nicotine in the isolated intestine of rabbits and guinea pigs. Cocarboxylase has the same effect as thiamine. The action of drugs stimulating sympathetic or parasympathetic nerve endings is not influenced by thiamine. This effect of thiamine is linked to the thiazole moiety of the thiamine molecule and appears to be analogous to the effect of certain sulfonamides. Thiamine also inhibits the action of nicotine in the striated muscle of frogs. The effect of thiamine upon the nicotine action is not influenced by prostigmine. The processes involved in the inhibition of the nicotine action in synapses and in end plates at the myoneural junction are discussed.

Clinical and Electroencephalographic Studies: Correlations of Mental, Electroencephalographic and Anatomic Changes in Cases with Organic Brain Disease. H. Strauss. Am. J. Psychiat., 101: 42, July, 1944.

One hundred cases with organic brain disease and delta activity in the electroencephalogram were studied for correlations of the psychiatric status with the electroencephalogram and anatomical localization. Such disturbances as memory defect, mental retardation, dullness, inability to concentrate, overactivity and inability to concentrate can occur without any delta activity or associated with a small amount of delta activity. Higher amounts of delta activity are present in the syndromes of clouded consciousness and facetiousness. In cases with sleepiness and clouding of consciousness the delta activity is more equally distributed over the brain than in cases with facetiousness where there is accentuation of the delta activity over both frontal lobes.

Facetiousness is associated with dysfunction, not afunction, of both frontal lobes with a smaller degree of dysfunction of other parts of the hemispheres. The electroencephalographic results in this respect are in good agreement with the fact that facetiousness was most frequently found in lesions restricted to the frontal lobes and not invading other parts of the hemispheres.

Primary and Symptomatic Amyotrophic Lateral Sclerosis. I. S. Wechsler, M. R. Saperstein and A. Stein. Am. J. M. Sc. 208: 70, July, 1944.

Based upon a study of 81 cases, the authors concluded that amyotrophic lateral sclerosis is not a single disease entirely dependent upon one etiologic factor and that, in general, the syndrome may be divided into two large groups, namely, *primary* and *symptomatic*. The primary and larger group may possibly be the result of selective deficiency; the symptomatic and smaller group may be the result of inflammatory processes, of vascular disease, and possibly of toxic agents. The primary runs a subacute course and terminates fatally in two or three years; the symptomatic are more chronic and may persist for many years. Lateral sclerosis and progressive spinal muscular atrophy are clinically and anatomically separate disease syndromes. There is no parallelism between the intensity of fibrillations and the severity of the disease or between the spasticity and hyperactivity of the deep reflexes and the presence or absence of the Babinski sign and the abdominal reflexes.

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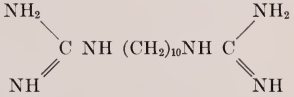
ON THE INFLUENCE OF STILBAMIDINE UPON MULTIPLE MYELOMA

I. SNAPPER, M.D.*

Stilbamidine[1] is a drug which in recent years has been used with great success in the treatment of kala azar. This disease is characterized by an increase of the globulin content of the serum. Since the globulin content of the serum is also frequently increased in multiple myeloma, we have tried stilbamidine since the beginning of 1945 for the treatment of multiple myeloma (1).

HISTORICAL REMARKS

The curative influence of stilbamidine in kala azar was described in 1939 by Warrington Yorke. The history of this discovery is interesting for it demonstrates how scientific knowledge may at times be advanced on the basis of wrong assumptions. It has been known since 1911 that trypanosomes require glucose for survival. This led Jansco' and Jansco' (2) in 1935 to try the action of a hypoglycemia-producing drug in experimental trypanosomiasis. They found that synthalin, a compound which causes hypoglycemia and which had once been used for the treatment of diabetes, has a definite therapeutic action on mice infected with trypanosomes. In 1937 Warrington Yorke and Lourie demonstrated that this action of synthalin is not related to the hypoglycemia which it causes (3). Insulin proved to have no influence upon experimental trypanosomiasis, and in addition, synthalin was found to exercise a trypanocidal action in vitro. These observations led to the study of varous compounds chemically related to synthalin.

Synthalin, decamethylene diguanidine, 

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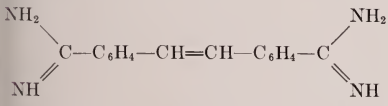
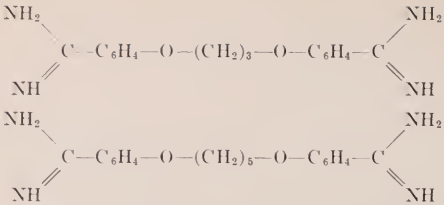
is characterized by two di-amidino groups linked with an aliphatic chain. Di-amidino compounds linked with an aromatic chain have been found to be even more strongly trypanocidal. The following three compounds were ultimately chosen for clinical experiments (4).



4:4 diamidino stilben or stilbamidine

*From the Second Medical Service of the Mount Sinai Hospital, New York.

[1]May & Baker (Manufacturers) Dagenham, near London. The stilbamidine used in this study was supplied by Merck and Co. Inc., Rahway, N. J. through the courtesy of Dr. D. F. Robertson.



4:4 diamidino dibenzoxy-propane or propamidine

4:4 diamidino dibenzoxypentane or pentamidine

Warrington Yorke and Lourie soon found that the therapeutic action of these diamidino compounds was not limited to trypanosomes but was also effective in experimental infections with certain malarial plasmodia and with piroplasms. In experiments performed at the request of Yorke, Adler and Tchernomoretz in Jerusalem observed that stilbamidine had a marked therapeutic action in Syrian hamsters infected with Leishmania donovani (5). The following year the first cases of human kala azar successfully treated with the same compounds were published (6, 7). Most of the current experience has been with 4:4 diamidino stilbene. Formerly the HCl salt of diamidino-stilbene was used. This has been replaced by the di-isethionate (di-β-hydroxy-ethane sulphonate) of diamidino stilbene because the latter is more stable and more soluble. This newer preparation of stilbamidine contains only two-thirds of the active compound compared with the HCl salt and for every 100 milligrams of the HCl salt, 150 milligrams of the modern preparation of stilbamidine must be used.

SIDE ACTIONS OF STILBAMIDINE

If the solutions are freshly prepared before use, no serious toxic reactions have been observed other than transitory vasomotor phenomena. The injections cause from time to time transient general itching and formication, which the natives appreciate as proof that a potent drug has been administered. The injection is usually followed by a fall in blood pressure which may, exceptionally, lead to sweating, dizziness, nausea, epigastric discomfort and even collapse. Some clinicians administer 0.25 cc. of 1 to 1000 solution of adrenalin subcutaneously, ten minutes before the stilbamidine injection, in order to prevent these vasomotor reactions (8). In the myeloma patients the side actions of the adrenalin injections were more troublesome than the slight fall in blood pressure caused by stilbamidine. Even so, adrenalin should always be kept on hand in case a stilbamidine injection causes a marked drop in blood pressure.

In a few of our patients where the vasomotor reactions were especially severe, an injection of 1/150 gr. to 1/200 gr. of atropine sulphate before the stilbamidine injection prevented the vasomotor reactions.

Just before use, stilbamidine is dissolved in 10 cc. distilled water and given by intravenous injection. These injections are occasionally followed by thrombosis of the injected vein. When the veins are poor, stilbamidine dissolved in 5 cc. o 2 per cent novocaine or procaine solution can be injected intramuscularly

One characteristic late sign of intoxication may occur several months after th

treatment, that is, dissociated anesthesia in the area of the trigeminal nerve (8). There may be loss of sensation to light touch whereas the sensations of pain, temperature and pressure usually are preserved. This facial anesthesia begins two and one-half to five months after the treatment has been stopped. It lasts a long time but gradually shows a tendency to spontaneous recovery.

During the war other signs of intoxication such as delayed liver degeneration were observed in Africa. It has been proved, however, that these side actions were due to the fact that at the time stilbamidine was being sent in solution from England to North Africa. During transport, chemical changes took place because stilbamidine which is sensitive to light was transformed to toxic products (9). If stilbamidine is injected immediately after it has been dissolved, no danger of liver damage exists.

In animal experiments, stilbamidine has been proved to have a depressing effect on the renal function and to increase the urea nitrogen content of the blood (10).

DOSAGE

Stilbamidine, and also propamidine and pentamidine have given excellent results to date in the treatment of kala azar in India, the Sudan and China. In the Sudan the majority of kala azar patients are resistant to the antimony derivatives which have for years been the usual anti-Leishmania drugs in India, China, etc. Stilbamidine has proved to be an excellent drug for such antimony-resistant cases of kala azar not only in the Sudan but also in the other parts of the world.

In kala azar usually ten injections of 150 milligrams of stilbamidine are sufficient to cure the patient. Several cases of kala azar have been reported in which much larger doses of stilbamidine were necessary before a cure could be obtained. These doses varied between 2.9 grams and 5.5 grams of HCl stilbamidine (equivalent to 4.4 and 8.2 grams of modern stilbamidine) administered in the course of four to five months (11).

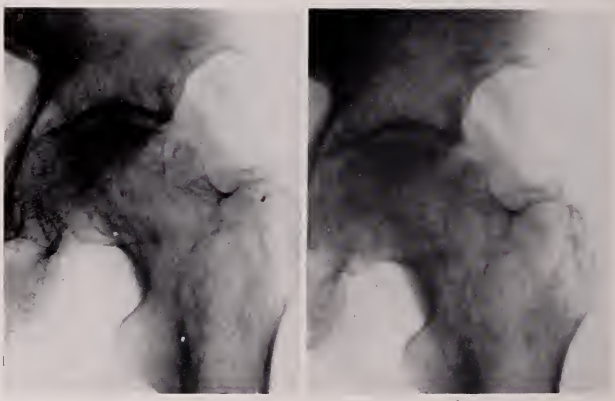
In the beginning the myeloma patients were treated with 15 injections of 150 milligrams of stilbamidine, given daily or every other day. More recently we have continued the treatment over a longer period and increased the total dose of stilbamidine given to five and six grams.

CLINICAL RESULTS

Stilbamidine* seems to have a specific influence upon the severe bone pain which is so frequently an outstanding symptom of multiple myeloma. Often after the 4th injection, sometimes later in the treatment, the patient's pain disappears. One has to be careful not to permit the patients to move around freely in this stage because the danger of pathological fractures of the diseased skeletal parts is still great. When the series of stilbamidine injections is finished, the bone pain usually does not recur. Patients with myeloma kidneys often do not react favorably upon the treatment. On the whole, stilbamidine treatment

* Only when combined with a diet poor in animal protein.

has given the best results in patients with widespread, but not large, osteolytic lesions and with normally functioning kidneys.



a b

Fig. 1a. J. G. Multiple myeloma. February 1945. Large bone defect at head of right femur.

Fig. 1b. J. G. Multiple myeloma. April 1946. After treatment with stilbamidine bone defect of head of right femur filled out.

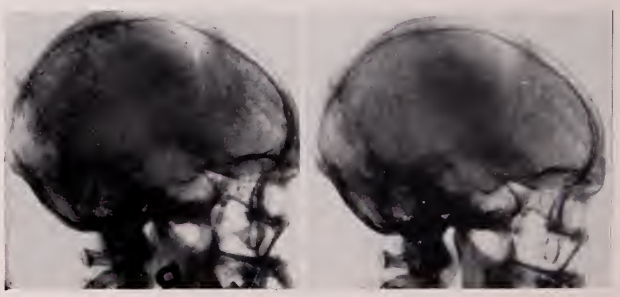


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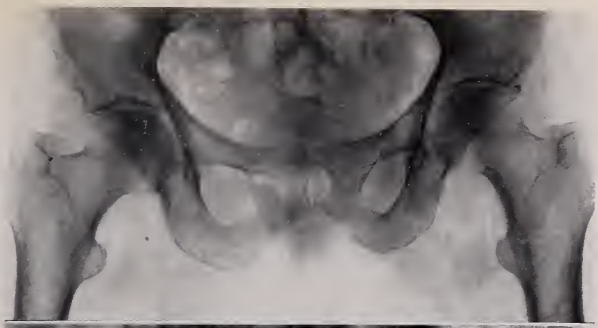
Fig. 2a. J. G. Multiple myeloma. February 1945. Skull riddled with small osteolytic myelomatous areas.

Fig. 2b. J. G. Multiple myeloma. April 1946. After treatment with stilbamidine no spread of the myelomatous process in the skull.

Two such patients treated with stilbamidine 16 months ago have been well and normally active since. Pathological fractures have healed. Some of the bone defects have filled out, in other areas recalcification has taken place. Most

a



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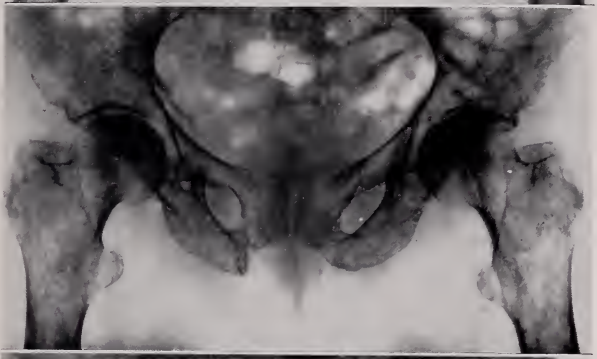

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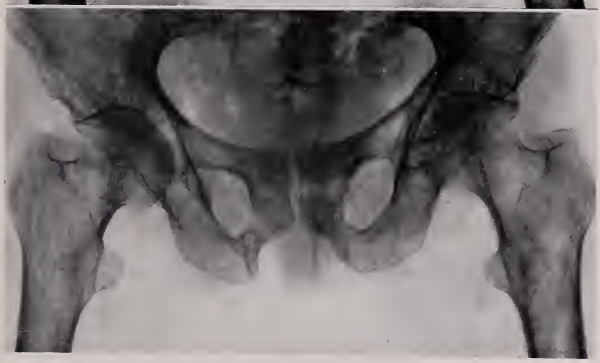
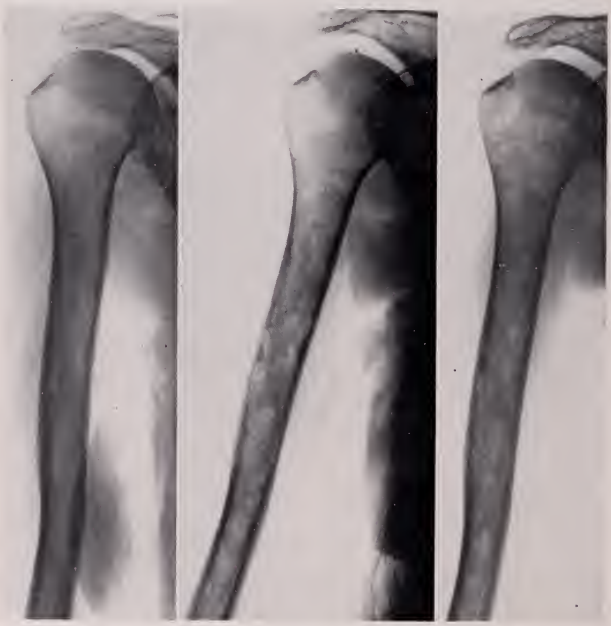


Fig. 3a. B. W. Multiple myeloma. October 1944. Pelvis. No significant lesions

Fig. 3b. B. W. Multiple myeloma. March 1945. Before treatment with stilbamidine. The disease has made rapid progress. Widespread dissemination of myelomatous areas in pelvis and femora. A complete fracture of the right os ischium with incomplete fractures of right and left os pubis just lateral to the symphysis.

Fig. 3c. B. W. Multiple myeloma. April 1946. After completing two courses with stilbamidine. Healing of fracture of os ischium and of incomplete fractures of os pubis. Recalcification of pelvis and femur.

of the osteolytic lesions can still be observed on the roentgenograms but none of the lesions have expanded. After the stilbamidine treatment the disease has evidently been arrested.



a b c

FIG. 4a. B. W. Multiple myeloma. Right humerus. October 1944. No significant findings.

FIG. 4b. B. W. Right humerus. May 1945. During treatment with stilbamidine. Rapid progress of the disease. Humerus is now riddled with myelomatous areas.

FIG. 4c. B. W. April 1946. After two series of stilbamidine. Reconstruction of the cortex and recalcification in many areas.

Figures 1a and 1b show the filling out of a gaping bone defect in a femur head; figures 2a and 2b the absence of expansion of the disease in the skull of the same patient.

Figures 3a, 3b and 3c illustrate the development of the disease in the pelvis of a second patient. Figure 3a is the roentgenogram taken six months before treatment; figure 3b in the beginning of the treatment. Comparison of these two roentgenograms shows that the disease was rapidly progressive before treatment was begun. Figure 3c is the roentgenogram taken 15 months after the stilbami-

dine treatment. The pathological fractures have healed, the bone defect in the pubic bone adjacent to the symphysis has filled in. Figures 4a, 4b and 4c illustrate the changes in the right humerus six months before treatment, during the treatment, and fifteen months after the treatment.

The marked clinical improvement is, therefore, accompanied by a certain degree of recalcification. Notwithstanding this remarkable change for the better, an anatomical cure of the disease is definitely not obtained. Even in these two patients who have done remarkably well, myeloma cells can still be seen in the bone marrow. In seven other patients who, for the time-being, are doing well, the excretion of Bence Jones protein in the urine and the increase of

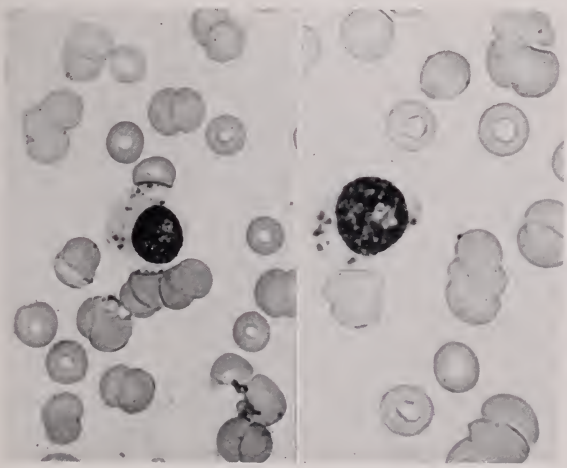


Fig. 5. B. W. Bone marrow smear of patient in the 4th week of treatment with stilbamidine. (Wright stain). Two myeloma cells containing many deeply stained confluent granules.

the globulins in the serum have not been influenced. Five of the fourteen patients, treated until now, have died.

HISTOLOGICAL CHANGES OF THE MYELOMA CELLS DEVELOPING UNDER INFLUENCE OF STILBAMIDINE TREATMENT

This clinical improvement under influence of the treatment with stilbamidine is accompanied by the following histological changes in the myeloma cells (12).

1. Myeloma cells have a basophilic protoplasm which is often vacuolated but does not contain granules. After four weeks stilbamidine treatment, Wright or Giemsa stains of bone marrow smears elicit the presence of large basophilic granules in the cytoplasm of the myeloma cells. After several weeks of treat-

ment these granules have a tendency to coalesce and ultimately may even resemble inclusion bodies (fig. 5).

2. Supravital stain with Janus green and neutral red of myeloma cells shows the presence of many green staining mitochondria. After stilbamidine treatment the supravital stain shows not only the presence of these mitochondria in the myeloma cells, but in addition, large red staining globules are found.

3. The cytoplasm of myeloma cells stains red with Unna's phenol methyl-green pyronine. After stilbamidine treatment this stain reveals the presence of brightly red granules in the cytoplasm.

4. These granules are not metachromatic as shown by staining with Unna's polychrome methylene blue.

5. These granules do not show positive oxydase reactions.

In one patient myeloma cells occurred in the peripheral blood. The above mentioned granules were also found in the circulating myeloma cells.

DISCUSSION

Altho the therapeutic results obtained by the administration of stilbamidine to patients with multiple myeloma are only limited, these morphological changes indicate that stilbamidine actually has an influence upon myeloma cells. These changes seem to be specific for myeloma cells because in none of the other elements of the bone marrow of the myeloma patients treated with stilbamidine can such granules be demonstrated. This may well explain why on the basis of our clinical trials stilbamidine has no influence at all upon diseases which seemingly are related to multiple myeloma as lymphatic leukemia, myeloid leukemia, and lymphomatosis. For completeness sake it may be added that this drug also does not change the course of carcinoma or of granuloma inguinale.

It must be stressed that even in the myeloma cells filled with large and confluent basophilic granules, apparent signs of degeneration do not develop. The nucleus and nucleoli conserve a normal aspect, the cytoplasm, apart from the abnormal granules, seems to remain intact. Also, as mentioned above, the myeloma cells do not ultimately disappear from the marrow and the signs of abnormal protein metabolism continue, even when 80 to 90 per cent of the myeloma cells contain considerable numbers of basophilic granules.

It has been possible to demonstrate that these inclusions in the myeloma cells contain ribose nucleic acid. In this connection the highly interesting in vitro experiments of Kopac (13) must be discussed. Kopac demonstrated that stilbamidine dissociates protamine ribonucleate and releases the protamines from these compounds. In vitro the interaction of stilbamidine and nucleoproteins results in the formation of insoluble stilbamidine-ribose nucleate complexes.

Until now it has been impossible to demonstrate the presence of stilbamidine in the granules which develop in the myeloma cells under influence of stilbamidine treatment. In this connection it may be important that stilbamidine was found in the myeloma tissue of one patient who came to autopsy.

Assuming that the reactions described by Kopac are responsible for the changes visualized in the myeloma cells under influence of stilbamidine, then the specifi-

city of the inter-reaction between stilbamidine and myeloma cells may, perhaps be understood. It is probable that the abnormal proteins which appear in the body fluids in most cases of multiple myeloma are formed in the myeloma cells. The differences between the proteins of the myeloma cells and the proteins of other cells could thus be the reason why stilbamidine can dissociate the protamine ribonucleate of the myeloma cells but not of other cells.

It will now be necessary to try and demonstrate the influence of other diamidines (propamidine, pentamidine) on the course of multiple myeloma. It is true that in the treatment of kala azar these compounds are just as active as stilbamidine. Kopac's experiments indicate, however, that as far as the hydrolyzing effect on protamine ribonucleate complexes is concerned, differences may exist between the different diamidines. Therefore, it seems not impossible that the action of other diamidines on the course of multiple myeloma may differ from the influence of stilbamidine.

SUMMARY

Injections of stilbamidine have a favorable influence upon the pains of many patients with multiple myeloma. In nine of fourteen cases an arrest of the progress of the disease has been realized. Two of our patients who were complete invalids before treatment was begun have resumed their normal activities for sixteen months. The disease is arrested but not cured since the bone marrow of these patients still contains considerable numbers of myeloma cells.

Favorable results have been obtained only in patients who followed a diet poor in animal protein. Animal protein evidently blocks the action of the drug as is indicated by the negative results of the stilbamidine treatment obtained in myeloma patients fed on a diet rich in animal protein.

Apart from this clinical improvement stilbamidine causes morphological changes in the myeloma cells. During the treatment large basophilic granules containing ribose nucleic acid appear in the cytoplasm which have a tendency to become confluent. None of the other bone marrow elements show the presence of comparable granules or inclusions. This may explain why stilbamidine has no influence upon the course of lymphatic and myeloid leukemia, lymphosarcoma, Hodgkin's disease,—also not on carcinoma.

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PRIMARY PULMONARY CARCINOMA*

Report of Two Cases

HAROLD NEUHOF, M.D.

The following two cases are illustrative of the fact that symptoms provoked by a metastatic lesion may be the first clinical manifestation of a primary lung carcinoma.

Case 1. History. (Adm. #539345) L. S., a man, aged 56 years, who complained of numbness, stiffness, and pain in the right side of his face for 4 months before admission, was admitted to the Neurological Service on September 13, 1945. Three days before admission the stiffness extended to the right side of his neck. Occasional diplopia was also noted. It is of particular interest that there were no pulmonary complaints.

Examination. There was a cystic mass in the right tonsil and a grape-sized, firm, nontender lymph node in the right supraclavicular area. There was bilateral papilledema as well as evidence of involvement of the 5th, 6th and 7th cranial nerves on the right side. The admission diagnosis was probable malignancy of the right tonsil, cerebral metastases and a metastic node in the supraclavicular region.

Course. The lesion in the tonsil proved to be a simple cyst. Biopsy of the right supraclavicular node showed metastatic anaplastic carcinoma. In this connection it is of interest to note that occasionally a suspected supraclavicular node may on surgical dissection prove benign whereas a deeper node not palpable on physical examination may be malignant. There are also instances in which a clinical picture leads to the impression that metastatic supraclavicular nodes should be present and such nodes are not palpable. Occasionally, a surgical dissection will reveal involved lymph nodes.

In this case the biopsy of the right supraclavicular node revealed metastatic anaplastic carcinoma. X-ray examination of the dorsal spine revealed a dense shadow which was situated behind the heart. Accordingly an x-ray of the chest was taken and this disclosed a density occupying the posterior half of the left lower lobe with some shrinkage of the lobe. It appeared reasonable to believe that this was the primary lesion, although the shadow could be regarded as distinctive of a cancer of the lung only in connotation.

Case 2. History. (Adm. #535688) N. L., a fireman, aged 35 years, suddenly experienced severe pain in the right shoulder some 6 months before he was admitted on June 14, 1945 to the Neurological Service. The severe pain persisted for a period of 3 weeks and was sufficiently acute to keep this patient from work. The pain disappeared as suddenly as it began but returned some 8 weeks before admission. This time, however, it persisted. The pain radiated down the arm and into the right side of the neck. There had never been any symptom referable to the bronchial tree or pulmonary parenchyma.

Examination. The patient showed weakness of the right deltoid, biceps and triceps muscles. X-ray of the cervical spine showed no abnormalities and the first x-ray of the chest was also normal. X-ray of the right shoulder revealed a destructive lesion situated in the neck of the scapula. A biopsy examination of this tissue revealed metastatic adenocarcinoma.

Course. Because of this finding a search for the primary focus was of interest. Intravenous pyelography and x-ray examination of the skeletal system revealed no abnormalities. A new x-ray of the chest now revealed a faint infiltration in the posterolateral portion of the right lower lobe which was regarded as the probable primary lesion. It was too faint to be recognizable from a distance and the x-ray film is therefore not shown. Subsequently, the infiltrations in the right lower lobe increased in extent and later a hemorrhagic effusion supervened, confirming the impression that the primary lesion was located in the lung.

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CERVICO-MEDIASTINAL INFECTION*

Case Report

ARTHUR H. AUFSES, M.D.

One of the causes of cervico-mediastinal infection is perforation of the esophagus. Whether this is due to a foreign body, such as a chicken or fish bone, or to an accident occurring at the time of esophagoscopy, the ensuing periesophageal infection is a most serious complication. Unless it receives prompt surgical intervention, a rapidly spreading phlegmonous mediastinitis occurs.

Whether the perforation occurs in the thoracic esophagus or in the cervical region is of little significance. The periesophageal tissue planes in the neck are directly continuous with the mediastinum and the infection travels rapidly from the cervical region into the posterior mediastinum with very little tendency to localize.

CASE REPORT

History: (Adm. #535251) A white porter, aged 63 years, was admitted to the Mount Sinai Hospital, on June 4, 1945, complaining of difficulty in swallowing. Seven months previously, he noticed that although fluids could be swallowed with ease, solid foods seemed to stick and had to be washed down with liquids. This was accompanied by epigastric pain during and after eating, and by gaseous eructations. While eating, he experienced a sensation comparable to that of a sac filled up beneath his breast bone and gradually decreased in size as the food passed through. He had forced himself to vomit occasionally, and noticed that the vomitus was not sour tasting. He had lost eleven pounds during these seven months.

He had had a similar episode of difficulty in swallowing five years before the present admission. At that time his symptoms, somewhat relieved by alkalies, had lasted for one year. X-ray examination at that time indicated a cardiospasm. He had been perfectly well in the intervening four years. In 1927 he had a cholecystectomy and appendectomy.

Examination: The patient's blood pressure was 144 systolic and 86 diastolic; hemoglobin, 78 per cent; white blood cells, 13,400. An electrocardiogram revealed "the pattern of a defective, atypical, right bundle branch conduction indicating myocardial involvement." X-ray study of the esophagus and stomach (made before admission) showed a narrowing of the lower end of the esophagus without any significant features to aid in the differential diagnosis between spasm and malignancy.

Course: An esophagoscopic examination was performed on June 7, 1945. After several difficult attempts to pass the esophagoscope, it suddenly fell into a cavity, which the operator at once recognized as being outside the esophageal wall. Although the patient did not complain of pain, and although there was no palpable subcutaneous emphysema, an x-ray examination was performed immediately. The films revealed air in the retroesophageal and retropharyngeal spaces, without definite evidence of widening of these spaces. Sulfadiazine and penicillin were administered immediately.

Shortly before the operation, which was performed three hours later, it was noticed that he was hoarse, and laryngeal examination revealed a paralysis of the right vocal cord, probably traumatic in origin. The cervical mediastinotomy which was performed on the left side disclosed air under tension in the fascial planes of the neck and in the retro-

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esophageal space. A tract was found extending into the superior mediastinum down to the arch of the aorta. This end of the tract was packed and further exploration exposed the

FIG. 1. Widening of superior mediastinum one week after cervical mediastinotomy.

FIG. 2. Lipiodol injected through cervical wound outlines mediastinal abscess.

perforation in the beginning of the esophagus. The opening was approximately three-eights of an inch in diameter, with everted mucous membrane. It was situated at the beginning of the esophagus on its posterior wall, slightly to the left of the midline. Methy-

lene blue given by mouth appeared immediately in the wound. The tract was followed prevertebrally to the right side of the esophagus, and the entire area was packed widely.

Following operation, the temperature remained slightly elevated for the first week. X-rays taken on June 13 showed a widening of the superior mediastinum (fig. 1). The esophageal perforation had closed spontaneously, and the patient was taking fluids by mouth without any leakage into the wound. Lipiodol instilled into the wound on June 18 showed a wide tract leading down into the posterior mediastinum to the level of the sixth rib posteriorly (fig. 2).

A posterior mediastinotomy was performed on June 20. The posterior end of the left fourth rib and transverse process were removed under local anaesthesia. The pleura was stripped away, exposing the mediastinum. No evidence of the mediastinal pocket could be found. The drainage tube which entered the mediastinum through the cervical wound could not be felt, and methylene blue injected through it could not be seen in the tissues.

FIG. 3. Lipiodol injected into thoracic wound. Mediastinal tract no longer visible.

Even a long artery clamp inserted through the cervical wound could not be felt. An iodoform packing was inserted into the depths of the wound to act as an x-ray marker, and the remainder of the wound was packed with plain gauze. In this manner, the pleural cavity was not entered and it was felt that new x-ray examination would be of value in demonstrating the relationship of the cervico-mediastinal tract to the thoracic exploration. These x-ray films did show that the approach had to be somewhat more mesial and directly in front of the bodies of the vertebrae.

Three days later, the posterior end of the third rib and its transverse process were excised, and the mediastinal pocket was then easily entered. Through and through drainage from the neck to the posterior mediastinum at the level of the sixth rib was established.

Following this operation, there was no longer any evidence of retention in the wounds, which showed signs of rapid healing. Despite an apparently well drained infection, the temperature did not return to normal but continued to reach 101°F. daily for the next two weeks. During this time, the patient appeared well and had no complaints. On July 17, lipiodol was instilled into the mediastinotomy wound in an effort to discover an undrained pocket, which might explain the continued fever. This x-ray examination showed that the

mediastinal tract was practically entirely healed, having been reduced to a small slit (fig. 3).

At this time, the patient again began to complain of severe dysphagia related to the lower end of his esophagus, and the daily temperature reached 103°F. Another x-ray examination performed on July 23, showed the mediastinal shadow to have returned to its normal limits. The cervical wound had completely healed by this time, and the mediastinal wound was reduced to a narrow sinus. The persistence of fever could not be explained. Blood cultures, as well as all other laboratory tests, were negative.

On July 27, abdominal examination revealed a large, hard liver, and it was now felt that the fever had been due to a malignancy of the lower end of the esophagus and stomach, with metastases to the liver. He was discharged on July 31, 1945.

COMMENT

This case illustrates one of the dangers of esophagoscopy, namely perforation. It also shows that in spite of very early surgical intervention, mediastinal infection can occur from a cervical esophageal perforation. It demonstrates the early spontaneous closure of the esophageal tear after surgical drainage, and, finally, that after the mediastinal infection has become localized it can be drained adequately and safely through a posterior mediastinotomy.

SPONTANEOUS PNEUMOTHORAX*

Report of Two Cases

H. HENNELL, M.D.

In many cases of spontaneous pneumothorax acute symptoms are precipitated by the complete collapse of the lung with displacement of the mediastinum toward the uninvolved side with resultant embarrassment of the uninvolved lung. This is particularly true when the intrapleural pressure on the pneumothorax side is considerably on the positive side during both phases of respiration—the so-called tension pneumothorax. The two cases to be discussed in this report presented a less dramatic clinical picture: the onset was mild in one case and relatively subacute in the other; and the involved lung in both cases was only partially collapsed by a low tension pneumothorax. The chief problem in these two patients was the persistence of the pneumothorax because of the recurrence of the mechanism which originally produced the entry of air into the pleural cavity. While the symptoms produced were not severe, they were, nevertheless, incapacitating to a greater or lesser degree. The patients required treatment because spontaneous recovery did not take place after months of so-called conservative therapy.

Case 1. History. (Adm. #538232) A tailor, aged 46 years, was admitted to the Mount Sinai Hospital complaining of a chronic cough for many years. The cough was most annoying in the morning, but not particularly incapacitating, so that he was able to attend to his business for about 10 hours every day. He came under observation in August of this year because of persisting dyspnea with acute exacerbations for about four months. The symptoms were severe enough to prevent him from carrying on his work.

Course. During those four months he was hospitalized twice. The diagnosis of spontaneous pneumothorax was made at the onset. He was treated by air aspirations for the relief of the acute dyspnea, and by blowing bottles in an attempt to reexpand the lung, but without success. The pneumothorax was not large and produced only a 50 per cent collapse of the right lung. However, there was marked emphysema with bleb formation also involving the healthy lung, which was the reason for the respiratory embarrassment caused by even this limited low tension pneumothorax. The patient was treated by the induction of a chemical pleuritis with a prompt and apparently lasting cure.

Case 2. History. (Adm. #534470) A man, aged 52 years, was admitted to the Mount Sinai Hospital complaining of shortness of breath. He had always enjoyed good health and participated in vigorous sports, including tennis and skiing. He had no antecedent pulmonary history. Early in February of this year, while skiing, he experienced a mild discomfort in the upper anterior chest. The chest discomfort became worse during the night and continued during the following day. When on the third day the discomfort persisted, he consulted his family physician who advised rest, attributing the complaint to the strain of the sport. A cardiac basis for the symptoms was suspected. However, x-ray examination a few days later finally established the diagnosis of spontaneous pneumothorax with 50 per cent collapse of the right lung. Because of the limited extent of the pneumothorax, he was assured that the condition was not serious. He was advised to rest for 2 to 3 weeks by which time the lung was expected to reexpand.

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During the ensuing 3 months the patient experienced recurring episodes of moderate chest pain with increased dyspnea every few days. During this time he was frequently subjected to fluroscopic examination and it was repeatedly noted that after partial reexpansion the lung would recollapse. The episodes of pain and increased dyspnea corresponded to the incidence of the recollapse of the lung. In order to corroborate the suspected mechanism, the patient's right pleural cavity was aspirated and about 800 cc. of air were withdrawn. This reduced the intrapleural pressure from −8, −2 to −14, −6 mm. of Hg. The lowered negative pressure was sustained for a 15 minute period of observation. One-half hour after the aspiration of the air the right lung could be observed fluoroscopically to retain its increased degree of reexpansion. However, a few hours later the patient again experienced the chest pain and increased dyspnea noted on previous occasions. When seen the next day, x-ray examination showed the right lung to have recollapsed and manometric readings showed intrapleural pressure to be −7, −2 mm. of Hg. Because of the tendency for spontaneous pneumothorax to recur, it was decided to hospitalize the patient and treat him by the induction of a chemical pleuritis. This was done, and the result was satisfactory, prompt and apparently lasting.

COMMENT

In the first case, the chronic pulmonary history explains the development of the emphysema with bleb formation which was apparent in both lungs. In the presence of numerous blebs one has no difficulty in supposing that the rupture of these blebs produced the spontaneous pneumothorax. One could further suppose that once the pleural surfaces were separated by the first pneumothorax other blebs tended to rupture as the pneumothorax was gradually absorbed and the intrapleural pressure became more negative. For the pressure inside the emphysematous bleb became relatively greater as the negative pressure in the pleura became more negative, and the visceral pleura was too weak to support this pressure gradient. By inducing a chemical pleuritis the visceral pleura was thickened and rendered more resistant to rupture. Furthermore, as the lung reexpanded and the visceral and parietal pleura touched and became agglutinated, the pleural space was obliterated and recurrences of spontaneous pneumothorax were thus prevented.

The chemical pleuritis can be induced by intrapleural injection of concentrated glucose (50 cc. of 67 per cent glucose). This is repeated every few days in order to maintain an active pleural reaction until reexpansion of the lung is completed. In our experience, 10 to 20 cc. of iodized oil can also be injected. This chemical is capable of producing a more active and sustained pleural reaction. The disadvantage of iodized oil is that it leaves residues which require many months or even years to be absorbed. Both these substances were employed in the two cases because of the tendency to repeated recurrence of the pneumothorax.

The mechanism by which the spontaneous and recurring pneumothorax took place in the second case is not as obvious. The patient had no antecedent pulmonary history and showed no signs of emphysema as evidenced by the x-ray examination performed when the lung was fully reexpanded. Of course, a negative film does not exclude the presence of areas of emphysema.

The mechanism can be explained in this case by hypothecating the following sequence of events: The respiratory effort while skiing led to rupture of some marginal alveoli (which are poorly supported as compared with the partitional

alveoli) with the production of pulmonary interstitial emphysema. This led to the establishment of mediastinal emphysema, and finally to rupture into the pleura with resultant pneumothorax. Once a pneumothorax is established, the marginal alveoli will tend to distend and form emphysematous blebs; these may rupture as the intrapleural pressure falls with the absorption of the pneumothorax, thus renewing it. Here also, chemical pleuritis will prove beneficial by thickening the visceral pleura first and later obliterating the pleural space when the lung is reexpanded and the visceral and parietal pleura meet and agglutinate.

Not all cases of spontaneous pneumothorax require this active treatment since many of them cure themselves by a similar mechanism—the spontaneous pleuritis which may occur when air enters the pleural cavity. Active therapy is indicated only when spontaneous cure fails to take place, as was the situation in the two cases presented.

LIVER ABSCESS WITH PERFORATION INTO LUNG*

Case Report

MAURICE S. HARTE, M.D.

History. (Adm. # 522362) M. W., a white male, aged 38 years, was operated upon 1½ years before admission to the Mount Sinai Hospital for a perforated peptic ulcer. His condition at that time was precarious; he was not removed from the operating table for one hour after completion of the procedure. Nineteen days later, incision and drainage was undertaken for what was thought to be a right subphrenic abscess. He then became asymtomatic. There was, however, persistant drainage from the sinus for a period of one and one-half years. Lipiodol was injected into the tract in an attempt to visualize the underlying lesion. It was found that there existed a meshwork of tracts which led both downwards and upwards (fig. 1). The lower tract as visualized in the films outlined hepatic biliary radicles (fig. 2). Barium was given by mouth to silhouette the stomach and duodenum; the lipiodol in the sinus tract did not reach the bowel (fig. 3). The tract which extended superiorly, however, pooled just under the diaphragm, then narrowed and entered the bronchial tree on the right (fig. 4). When questioned again, the patient admitted coughing up oily material when the lipiodol injection was performed. There was no recollection of any other episode of cough or expectoration. The patient was admitted to the Mount Sinai Hospital on July 5, 1944.

Operation. (Dr. H. Neuhof) The tract was injected with methylene blue, split open, and explored. The network of tracts was coalesced into a sizable cavity which was found to be lined by necrotic liver tissue. One tract led upward toward the diaphragm and another into the liver substance. The upper tract was adequately opened and packed. The lower tract was only partially opened because of its varying ramifications and the rather brisk hemorrhage. The wound was packed widely open.

Course. Following the operation the patient became septic for the first time, with a spiking type of temperature curve. The wound discharged but little and the fever persisted. However, about two weeks later the sinus spontaneously drained two ounces of pus. Another exploration was performed resulting in the drainage of an additional small recess. The patient, however, continued to run a septic course. There was no response to either the sulfonamides or penicillin. The organism isolated from the pus was *hemolytic staphlococcus aureus*, twenty times as resistant as the standard organism to penicillin. In spite of the resistance only the standard dosage of 15,000 units every 3 hours, intramuscularly, could be used because of the difficulty in obtaining penicillin.

About two weeks later, a small bead of pus was seen on the lateral wall of the sinus tract. A curved forceps was thrust into that site and a very large hepatic abscess was entered from which about eight ounces of pus were evacuated. Despite the apparent adequate drainage, there was only temporary subsidence of the septic course. In the second month of hospitalization, an area of shifting dullness and tympany was found anteriorly at approximately the upper level of the liver. On the supposition that this might represent an undrained subphrenic abscess the patient was aspirated and a droplet of pus was obtained. Exploration was undertaken anteriorly. This proved to be a tiny liver abscess probably of no great significance. Therefore aspiration was immediately performed posteriorly where a substantial quantity of pus was obtained. Posterior drainage with the evacuation of a large liver abscess cavity completed the operative procedure. The possibility that this

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abscess may have communicated with the subphrenic space was considered but could not with certainty be determined.

Improvement followed but was temporary. The wound drained profusely at first but the septic course persisted. Repeated x-rays with lipiodol injected into the sinus tract had been taken periodically but never after the original films were any ramifications outlined

Fig. 1

Fig. 2

or could any extension to the lung be demonstrated. Two weeks later the patient was found to be disoriented, asphasic, and afflicted with a transient facial palsy. This was felt by some to indicate metastatic brain abscess. However, the episode was only transient and inasmuch as it was associated with high fever, the cerebral picture might have been attributed to toxicity. During the next few days, the general condition deteriorated

rapidly; the patient became moribound. At this point penicillin was again made available. The patient seemed so close to death that only with enormous dosages of penicillin could there be any hope at all. 500,000 units of penicillin were given daily with remarkable response. The temperature no longer spiked, fell rapidly, although never completely, to the normal level and the state of nutrition materially improved. After two weeks of therapy

Fig. 3

Fig. 4

the supply of penicillin was exhausted. Several days after discontinuance of the drug, high spiking fever recurred. The patient's decline was even more rapid than previously. He died two weeks after penicillin was discontinued, exhibiting toward the end the same type of cerebral picture which had been manifest earlier in the course of the disease. A full autopsy was obtained.

Postmortem. A huge multilocular hepatic abscess with persistant hepato-bronchopulmonary fistula into the right lower lobe bronchus was found. Multiple brain abscesses, both recent and older, were present. Pulmonary edema probably was a terminal factor.

COMMENT

In retrospect, it may be said that had sufficient penicillin been available the toxicity could perhaps have been controlled long enough to permit successful surgical intervention upon the remaining liver abscess. The fact that there was evidence of healing in the earlier crop of metastatic cerebral foci leads one to believe that the newer crop might also have resolved under penicillin therapy.

It is noteworthy that with the persisting perforation into the right lower lobe bronchus there were no pulmonary symptoms nor could the lipiodol gain entry into the bronchial tree throughout the postoperative course.

SPONTANEOUS RECOVERY FROM SUBACUTE BACTERIAL ENDOCARDITIS IN INTERVENTRICULAR SEPTAL DEFECT

JENNY STRICKER, M.D.

Spontaneous recovery from subacute bacterial endocarditus is a relatively rare occurrence. A report of such recovery from this disease in a patient who has been under observation for a period of ten years, therefore, seems worthy of presentation.

CASE REPORT

History. B. R., an 11 year old girl was first seen in December, 1936. At the time of her birth she had been found to have congenital heart disease. She developed normally and except for measles, pertussis and chicken pox she had no serious illnesses. For an indefinite period of time prior to this examination she had sticking pain in the left upper abdomen and had lost weight (8 pounds). Nine days before she was seen by her physician and shortly after she had her teeth cleaned by a dentist, she developed a mild sore throat associated with a rise in temperature to 102°F. Her fever subsided but after five days she had another rise in temperature accompanied by a chilly sensation and a slight cough. Her temperature would rise in the morning to 101°F., would fall below 100°F. in the afternoon and rise again to 103°F. at 10 o'clock at night.

Physical examination. The patient was a well developed pale girl appearing acutely ill but alert and cooperative. She appeared to be underweight. A rough, long, rumbling systolic murmur was audible all over the precordium, loudest in the third interspace just to the left of the sternum. The lungs were clear; the abdomen was soft; the spleen was enlarged two centimeters below the left costal margin. The liver was at the costal margin. There were no petechiae, and the fingers were not clubbed. On fluoroscopy the left ventricle was enlarged.

The diagnosis of an interventricular septal defect and subacute bacterial endocarditis was made and she was referred to the Mount Sinai Hospital.

Course in the Hospital. Four blood cultures on different occasions showed colonies of Streptococcus viridans. The hemoglobin was 66 per cent; the red blood cell count, 3,420,000; the white blood cell count, 6,800; the differential count: 62 per cent polymorphonuclears, 4 per cent eosinophils, 1 per cent basophils, 28 per cent lymphocytes and 5 per cent monocytes. The sedimentation rate was 30 minutes for 18 millimeters. Schick and tuberculin tests were negative. The temperature was septic, ranging between 99°F. and 104°F., except for a five day remission following a blood transfusion donated by the patient's mother. She received four transfusions in all. She was given prontosil without any effect. The child remained in the hospital three months. During that time she twice developed a cough accompanied by rales and a friction rub over the right lower lobe. These manifestations were thought to be due to embolic pulmonary infarction and this was verified by x-ray examinations of the lungs. When the patient was discharged at the request of her mother, her daily temperature rise still took place.

Follow up. One year after hospitalization she was reexamined. She had spent most of the year in the country and had gained twenty-four pounds. On occasions she had mild shoulder pains and her temperature rose to 102°F. This lasted only a few days. She had no chills. On examination a rough systolic murmur was noted at the third interspace to the left of the sternum. There were no petechiae nor clubbing of the fingers. The spleen was not palpable. There was a two plus albumin reaction in the urine. In the course of

another year she continued to gain weight. She attended school and now dieted to lose weight. There was no fever and no change on physical examination. In November 1940, four years after the first examination, the sedimentation rate was 90 minutes for 18 millimeters. The hemoglobin was 75 per cent. A red blood cell count was 4,600,000. The white blood cell and differential counts were normal. A blood culture was negative. During the following five years regular yearly re-examinations showed that she remained well and led a normally active life. She worked steadily and was doing additional voluntary work. She was asymptomatic when last examined on October 16, 1945.

COMMENT

Congenital anomalies are next in importance to rheumatic valvular deformities as factors predisposing to subacute bacterial endocarditis. In this case, as in most congenital anomalies, the endocarditis was right sided as evidenced by the pulmonary infarction. Of the grosser congenital abnormalities, a patent ductus is associated most often with bacterial vegetations. Less commonly subacute bacterial endocarditis occurs in cases with ventricular septal defect, coarctation of the aorta or lesions of the pulmonary orifice.

The first report of recovery from infective (streptococcal) endocarditis was published by Hemsted (1) in 1913. The patient, a female twenty one years of age, had a congenital interventricular septal defect. Following a tooth extraction she developed intermittent septic temperature and innumerable pulmonic infarcts. Streptococcus salivarius was isolated from the blood on several occasions. After one year's illness the patient recovered completely. She was treated with autogenous vaccines and autogenous serum. In 1937 Chester (2) reported a case of spontaneous recovery from subacute bacterial endocarditis, superimposed on a patent ductus Botalli.

Up to 1941 Libman (3) reported twenty five cases or 2 per cent of spontaneous recoveries in a series of 1260 cases of subacute bacterial endocarditis in adults. One died of renal insufficiency due to hypertension twenty three years after recovery from subacute bacterial endocarditis.

In a personal communication Dr. Murray H. Bass (4) reported a case of spontaneous recovery from subacute bacterial endocarditis, superimposed upon a patent ductus arteriosus. The blood cultures revealed Streptococcus viridans on three occasions. A bad prognosis was given and it was suggested that the patient be taken to Florida. This was done and when he returned three months later his blood cultures were sterile and his temperature was normal, indicating spontaneous recovery. Five years later his patent ductus arteriosus was ligated.

SUMMARY

A case of spontaneous recovery from streptococcus viridans endocarditis superimposed on a congenital patent ventricular septum defect is reported. The patient has remained well for ten years.

I wish to thank Dr. Ernst P. Boas and Dr. Murray H. Bass for permission to report this case.

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ESSAYS ON THE BIOLOGY OF DISEASE[1]

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Chapter 15

LIBMAN-SACKS DISEASE

This malady which has a long life cycle, lends itself well to a discussion from the dynamic viewpoint because it is compounded of a wide variety of clinical phenomena ranging from a larval or primitive type to a more or less complete form, between which various symptom complexes arise that have been viewed as separate disease entities. Death by no means awaits the completion of the clinical picture; inasmuch as the disease may be latent for years, death may occur at what appears to be a larval stage. The disease is so widespread throughout the human frame and the clinical expression is so protean that even in its incomplete form, accurate recognition as a rule, is possible. While the specific morphological background, the indeterminate verrucous endocarditis, is often missing and while there is sometimes difficulty in correlating clinical with morphological data and vice versa, nevertheless, taken together, these data represent an entity so sharply circumscribed as to justify this eponym as a distinct disease, even before the unknown cause is discovered.

The early or larval clinical evidences of Libman-Sacks disease. This malady is remarkably sex linked. According to Baehr (1) males are affected in only 5 per cent of all cases. The predominant age occurrence is between the 11th and 40th years. It is most common in the third decade. In Klemperer, Pollack and Baehr (2) the first series of 20 cases were all females. The youngest patient was 7 years old; the oldest 40. The disease is insidious and varies widely in respect to the earliest clinical evidence.

A. *Polyarthritis.* This was the first symptom in 9 cases. Frequently, there is a history of pains in multiple joints dating for months or even years before debilitating symptoms arise; in one instance 11 years. It cannot always be determined whether fever accompanied these attacks; under any circumstances, the diagnosis of "rheumatic fever" is often entertained. As a matter of fact, this diagnosis in some instances may very well be justified, because in a fair proportion of cases of Libman-Sacks disease that come to autopsy, rheumatic verrucous endocardial lesions are associated. This occurred in 5 of 23 hearts in Libman-Sacks disease examined by Gross (3). No joint or group of joints appear specially predisposed; the involvement is general. There are very few patients that escape polyarthritis some time in the course of the disease.

[1] This is the fifteenth chapter in a series of essays by Dr. Eli Moscheowitz, in which an attempt will be made to interpret certain forms of chronic disease from the biologic viewpoint, as opposed to the current trend toward rigid classifications implying a concept of disease as a more or less static phenomenon.

According to present plans, these essays will appear in consecutive issues of the Journal of The Mount Sinai Hospital. When the publication of the projected series of essays is completed, the several installments will be assembled and printed as a monograph.—Ed.

Indeed so frequent is the onset of Libman-Sacks disease heralded by what appears to be an "infectious arthritis", that the possibility of Libman-Sacks disease must be kept in mind, especially if it occurs in a young woman in whom no cause for the infectious arthritis can be discovered. Other clinical evidences of Libman-Sacks disease should be sought for, such as glandular enlargement, albuminaria, an unexplained patch of erythema, etc. Such circumspection has at times permitted an early diagnosis.

In one case that I recall the diagnosis of Felty's syndrome was considered because of an associated anemia, leucopenia and a palpable spleen. Later, the patient developed typical evidences of Libman-Sacks disease. More often, the polyarthritis is acute or subacute and is accompanied by fever. There is often a history of a number of such exacerbations before evidences of other visceral involvement set in, with prolonged intervals of remission, during which the patient feels practically well. I recall such a patient a young woman in her twenties, who was treated with gold. At the end of a few doses a violent high fever arose accompanied by an exacerbation of the polyarthritis and a generalized erythema multiforme which had the conformation of a butterfly lesion on the face. The gold was stopped and at the end of two weeks the fever and the erythema completely disappeared. A year later she died in another hospital of typical Libman-Sacks disease.

In contradistinction to rheumatic fever, the arthritis, according to some writers, leads to deformity if the disease is sufficiently prolonged (4). Baehr (37) has not observed this eventuality. Usually, the malady is not sufficiently prolonged to lead to such a result.

In summary, Libman-Sacks disease masquerades at times as a polyarthritis, acute, subacute, chronic or remittent, with or without deformity. Gyorgy (5) suggests that Still's disease in children may sometimes represent an incomplete manifestation of Libman-Sacks disease. This suggestion is founded upon the close clinical similarity between the two diseases. According to McCune (6) Still's disease is characterized, in addition to polyarthritis, by fever, glandular enlargement, secondary anemia, cutaneous manifestations and occasionally albuminuria. An additional similarity is evidenced in the frequency of an associated pericarditis; furthermore, according to Dawson (7) Still's disease is twice as common in females as in males. The possibility of such a mutation is suggested by the case report of Bayles (8) of a girl aged 12 who was diagnosed as Still's disease and who at post-mortem showed a non-constricting adherent pericardium without endocardial lesions and without Aschoff bodies. Unfortunately, the morphological findings in other organs are not reported. Inasmuch as there is doubt whether Still's disease is a disease entity or only a manifestation of rheumatoid arthritis in children, it seemed pertinent to investigate whether some cases of the adult type could be regarded as mutations of the Libman-Sacks disease, especially as pericardial and endocardial lesions have been reported as frequently associated in rheumatoid arthritis. Available data furnishes only suggestive evidence. Baggenstoss and Rosenberg (9) reported the high incidence of 56 per cent "rheumatic" lesions in 25 cases of rheumatoid arthritis. In

all but 2 Aschoff bodies were found. The pericardium was affected in 5 instances, in 2 with associated rheumatic endocarditis. In three it was the only structure involved, in one with a fibrinous, in the second with a fibrinopurulent exudate, and in the third the pericardial cavity was completely obliterated. Regrettably, the presence or absence of Aschoff bodies was not noted in the cases in which the pericarditis was the isolated lesion, nor are the case histories given or the histological findings in other organs. Bayles (8) found 6 rheumatic endocarditides in 23 cases of rheumatoid arthritis. In two others an isolated non-constricting healed adherent pericardium was present, without Aschoff bodies. One we have already quoted as having been diagnosed as Still's disease. The second, was in a woman aged 72 who gave no history of rheumatic fever; other data are lacking. As in Still's disease, there are certain parellelisms between adult rheumatoid arthritis and Libman-Sacks disease. Dawson (7) states that rheumatoid arthritis occurs three times as often in females as in males and almost always during the child bearing years. Enlarged glands occur in 53 per cent of all cases, there is a secondary anemia, and the incidence of pericarditis and adherent pericardium is 7 per cent. Pleuritis is common. Morphologically, Dawson finds vascular lesions with fibrinoid swelling, and fibrinoid changes throughout the ground substance of the mesenchyme, changes which have a striking similarity to those found in lupus erythematosus by Baehr, Klemperer and Pollack.

The evidence we have submitted is significant and suggests that there may be a common factor in both Libman-Sacks disease and certain instances of rheumatoid arthritis. The facts are sufficient to warrant a more complete study.

B. *Lupus erythematosus* is the next most frequent early manifestation of Libman-Sacks disease. Although Kaposi in 1872 recognized that lupus erythematosus was not strictly speaking a local manifestation of the skin but a symptom of a disease with a widespread visceral involvement which often leads to death, this fact was not widely recognized until the publication of Libman-Sacks (10) in 1924. In Klemperer, Pollack and Baehr's series of 20 cases, lupus erythematosus was the earliest symptom in 5, in every instance in the disseminated form, but often preceded by the discoid type. For a while, it was problematical whether the discoid and disseminated form of lupus erythematosus were distinct entities, but inasmuch as the discoid type passes into the disseminated, and less frequently, vice versa, (11), the probability is strong that they are simply variants of one and the same process. Baehr (37) has not observed these transitions. Whether the discoid type eventually always passes into the disseminated type is not definitely known, because the life cycle of Libman-Sacks disease sometimes covers a period of many years. Reports of "cure" of the discoid type, even for a period of years after the onset, must be viewed with reserve. For instance, Stickney and Keith (12) report a case in a woman who died at the age of 35 of Libman-Sacks disease. When she was 23 she had a discoid type of lupus erythematosus which remained healed for 11 years after therapy with quinine. At the age of 34 the eruption returned (after a sunburn) in a disseminated form; one year later she died. Not infrequently there is a history of recur-

rence of the discoid lesion with periods of remission. Case 4 of Klemperer, Pollack and Baehr's series showed a discoid lesion 9 years previously; it disappeared spontaneously but returned during the following 3 summers after exposure to the sun. Gold therapy was repeated after each recurrence. The year before she died, the rash reappeared in a disseminated form. Guion and Adams (13) report a patient in whom a typical butterfly rash appeared 9 years previously which reappeared each spring for the next 4 years, when it became disseminated. While generalized visceral involvement is usually associated with the disseminated form of lupus erythematosus, we have observed cases of discoid lupus in which evidence of visceral involvement are associated, for instance in the form of an albuminuria or general glandular involvement. Generalized Libman-Sacks disease with death may even ensue when the lupus remains discoid, as in the case of Edelman (14). Perhaps, this patient's severe thrombocytopenic purpura, a not infrequent complication of Libman-Sacks disease, caused his death before the discoid lesion could become generalized. The very frequent history of the development of the rash after exposure to the sun may hopefully furnish the clue to the origin of the disease. Unfortunately, studies in this direction have proven inconclusive. Ludy and Carson (15) found hematoporphyrin in a large percentage of his cases of lupus erythematosus, which they ascribed to lead infiltration of the skin. Keil (16) also speculates on the possibility of lead poisoning as a factor, but the evidence, both for the hematoporphyrinuria and the indictment of plumbism is unconvincing. Attempts at treatment of Libman-Sacks disease by shielding patients from ultra violet light have not been satisfactory, perhaps because when hospitalized these patients are already in the advanced stages. In the past few years, we have found that patients with Libman-Sacks disease appear to develop a deeper and more lasting skin erythema after measured doses of ultra violet light than in controls. However, the method is still too crude and we hope to introduce a finer method shortly. This test may prove useful in early diagnosis, for instance in cases that present polyarthritis without other lesions. In one instance, this test proved of value.

The feature that has always puzzled students of Libman-Sacks disease is the occasional absence of either the discoid or disseminated forms of lupus erythematosus throughout the entire life cycle of the disease. This can be satisfactorily explained if we visualize lupus erythematosus not as the disease itself, but as a specific dermatologic reaction to an unknown agent. It is a facultative but not a necessary symptom of a generalized process, and would bear the same relation to Libman-Sacks disease as a specific rash in an infectious disease. In some infectious disease, the specific rash is sometimes absent, but this does not invalidate the diagnosis. Nevertheless the cause for the mutations, the remissions and the occasional absence of the lupus lesions in Libman-Sacks disease are entirely unclear. While sunlight often is the activating agent, one must assume a predisposition, the nature of which is a complete mystery. There is no evidence for assuming a constitutional factor unless one regards femaleness and the child bearing age period as parts of a constitution.

Lupus erythematosus is not the only lesion of the skin that the Libman-Sacks disease may present.

C. *Purpuric lesions* of various types are common. Libman and Sacks called attention to such lesions in their original paper. These purpuric lesions may be in the nature of white centred petechiae, which at once distinguishes Libman-Sacks disease from rheumatic fever, in which white centred petechiae never occur. These white centred petechiae appear to be directly correllated with the presence of indeterminate verrucous type of endocarditis. In exceptional instances, the white centred petechiae may arise from a complicating vegetative bacterial endocarditis. This occurred in 4 of the twenty cases reported by Klemperer, Pollack and Baehr. Another common form of purpura may simulate purpura hemorrhagica, the Henoch-Schoenlein purpura, or Frank's capillary toxicosis (17). In most such instances, the purpura is the result of thrombocytopenia, due to great reduction in blood platelets (18, 14, 19 20). This form of purpura may indeed be the first presenting sign of the Libman-Sacks disease. In one of Keil's 2 case reports a splenectomy was performed because of suspected purpura hemorrhagica; 10 months later, the patient developed a disseminated lupus erythematosus, ending in death. Finally, a lesion of the skin may arise that is identical with erythema multiforme, (21, 22, 23) and such instances have been classified under the heading of Osler's "erythema with visceral manifestations". Indeed Libman (24) in reviewing Osler's report of his 29 cases finds that two were probably cases of Libman-Sacks disease, since Osler refers to heart murmurs, rheumatic joint pains and a terminal nephritis.

Whether some of these various skin lesions are due to direct vascular damage is altogether probable. Klemperer, Pollack and Baehr describe collagen changes amounting in places to fibrinoid degeneration, which may affect the smaller vessels. In this connection, it is essential to speak of the lesions in the mucosa of the mouth that are frequent in Libman-Sacks disease. These are small, round or irregularly shaped shallow ulcers, often with dirty brown edges, situated on the palate or buccal mucosa, the tonsil or the tongue. They may be accompanied by small petechiae. They sometimes bleed. In association with other evidences of disease their presence may be of diagnostic significance.

Acute arthritis and the skin lesions therefore are by far the commonest initial signs of Libman-Sacks disease accounting for 14 of the 20 cases reported by Klemperer, Pollack and Baehr.

D. *Nephritis.* In two of the 20 cases the initial presenting symptom was nephritis as evidenced in one case by ankle edema, a marked albuminuria and hypertension, and in the second by the discovery of a profound albuminuria. When the rare opportunity comes to follow the course of the illness from the discoid lupus phase to the disseminated, one finds that albuminuria is a late development. In these two cases therefore, the disease must have been dormant for a considerable period. In the later phases of Libman-Sacks disease, albuminuria occurs almost uniformly. Albuminuria and expecially its precursor, microscopic hematuria, may serve as a diagnostic aid in the presence of other suggestive signs of Libman-Sacks disease; and is particularly significant if hyper-

tension is absent, for hypertension is exceptional in Libman-Sacks disease. The hematuria and albuminuria can usually be correllated to renal vascular alterations. This will be discussed later. Exceptionally there is a true glomerulonephritis. This occurred in 2 of the 20 cases reported by Klemperer, Pollack and Baehr. The albuminuria is usually accompanied by a renal insufficiency of moderate grade, the blood urea rarely approaching uremic levels. Hypoproteinemia is not unusual and may give rise to anasarca.

E. *Fever.* In one patient fever was the presenting symptom. Fever is the most consistent sign in the terminal phases of Libman-Sacks disease, and was present in 100 per cent of Klemperer, Pollack and Baehr's series. The fever may be unassociated with visceral changes but usually it accompanies either polyarthritis, serositis or pneumonia. There is a tendency to remissions with the subsidence of these evidences. In the terminal phases, the fever is continuous, sometimes attains excessive heights without causing profound subjective disturbance and the curve is completely irregular.

F. *Raynaud's syndrome.* The onset of the disease was ushered in in one of the 20 patients by this syndrome which persisted two years and was then followed by a butterfly rash and arthritis. I observed many years ago a Raynaud's syndrome in a male patient with disseminated lupus erythematosus who was discharged from the hospital and whose fate is unknown. One of the patients reported by Guion and Adams (13) presented the same symptom. Raynaud's syndrome in Libman-Sacks disease is attributable to the vascular lesions.

In the 20th patient, the early history was that of a cough with pain in the chest and fever of some years standing. The cough increased in intensity eight months before admission. This was followed by chest pain and a rash on the neck which followed exposure to the sun. She died five days after admission to the hospital and at post-mortem a bronchiectasis and pneumonia were found, and both the atypical verrucous and rheumatic endocarditis. Inasmuch as the previous data are insufficient to determine the sequence of events, one cannot decide whether the bronchiectasis was independent or followed the pneumonia. This patient was evidently almost moribund when she became hospitalized. We shall discuss the pulmonary complications of Libman-Sacks disease in a subsequent part of this communication.

In this review of the beginnings of the Libman-Sacks disease, we have covered the natural history of an appreciable proportion of the clinical expression of the disease. There are however other phenomena that may occur in various phases of the malady.

G. *Enlargement of the spleen* is only exceptionally sufficient to render it palpable. In only 3 of the 20 cases was the weight more than 300 grams. The most characteristic morbid change is a peculiar periarterial fibrosis limited to the central and peniciliary arteries. This was present in 19 of the 20 cases. Klemperer, Pollack and Baehr regard this lesion as almost specific for Libman-Sacks disease because they did not find it in a diversified control series. Kaiser (25) found this lesion in 15 of his 18 cases, and in a control series found the same lesion in a less pronounced form in only 3.2 per cent. Significantly, he found the

same lesion in four cases of thrombocytopenic purpura. In view of the fact, as we have shown, that thrombocytopenic purpura may be the earliest evidence of lupus erythematosus a follow up of these four cases might prove fruitful. Despite the apparent non-specificity of these perivascular fibrotic lesions, the high incidence in Libman-Sacks disease may be of pathologic diagnostic importance in cases that reveal a paucity of other lesions.

H. *Lymph node* enlargement was present in 9 of the 20 cases. While such enlargement may be manifest in the earliest phases, it is not sufficiently pronounced to warrant attention on the part of the patient. Enlargement of the lymph nodes is usually first noted in the cervical region (26). Morphologically there is distortion of the lymphoid architecture, edema, swelling of the lymph sinuses, hyperplasia of the endothelial cells, occasionally areas of necrosis and collagen changes such as are found in other organs. The areas of necrosis have been mistaken for tubercles. Fox and Rosahn also occasionally noted a perivascular fibrosis comparable to that found in the spleen.

I. *Myositis and dermatomyositis.* Painful muscles of the extremities occasionally with atrophy that is not due to peripheral neuritis are common in intermediary or advanced phases. In 5 cases Klemperer, Pollack and Baehr found moderate perivascular infiltration. In a sixth case there was intense interstitial and perivascular infiltration associated with myolysis of the psoas and rectus muscles. Keil (27) reports five cases in which he noted transitions of the lupus lesions to sclerodermatous-like thickening of the skin with pigmentation. In each instance there was a coexisting myositis. In some a biopsy showed edema of the muscle fibres with loss of striae, fibrous and perivascular leucocytic infiltration. He ascribes the lesions to vascular disease. Inasmuch as dermatomyositis is only a symptom complex the result of a number of mechanisms, Keil's observations show that lupus erythematosus may be one of the backgrounds.

J. *Ocular findings.* Retinal exudates, hemorrhages, papilledema or a postneuritic atrophy are among the ophthalmoscopic findings seen in Libman-Sacks disease. Either one or the other or combinations are usually seen in the late phases. The only report of the histology of the retinal changes is that of Goldstein and Wexler (28) who found atrophy of the walls of the retinal vessels with replacement by hyalin, and occasionally perivascular fibrosis. The ophthalmoscopic picture, which is by no means uncommon in Libman-Sacks disease, closely resembles that found in the malignant phase of hyperstension. Inasmuch as hypertension is exceptional in Libman-Sacks disease, such findings are of crucial diagnostic value in suspected cases.

K. *Central nervous system.* Libman (24) calls attention to peculiar convulsive seizures that occur in the late stages, in one of which the patient may die. In addition stupor and sometimes palsies may occur. The causes for these symptoms is not known, because little is known of the morbid anatomy of the cerebrospinal nervous system in this disease.

L. *The blood.* We have already referred to the thrombocytopenia. In addition there is nearly always a secondary anemia and a leucopenia. Blood

cultures are always negative, unless there is a superimposed infection. This will be discussed more fully in a subsequent part of this paper.

M. *Serositis.* A pleurisy with or without effusion may occur in the early stages, but usually it accompanies the intermediate and terminal phases. It may be recurrent with periods of remission. Usually pleural involvement is accompanied by fever. A pleuritis may be independent or may accompany pulmonary involvement. The latter event is often terminal. Morphologically, the pleuritis reveals nothing distinctive.

N. These remarks apply as well to the *pericarditis*, except in the fact that effusion is less frequently seen. The presence of a pericarditis is highly significant diagnostically and should be sought for in a doubtful case. Very often its presence establishes the diagnosis. It is especially important in the differentiation of Libman-Sacks disease from subacute bacterial endocarditis, in which a pericarditis is exceptionally rare (Libman, 24). A pleuritis and pericarditis frequently coexist.

Peritoneal involvement occurs but is rare. It probably accounts in part for the abdominal pains that occasionally occur in every phase of the disease, and occasionally for ascites.

N. *Pulmonary involvement.* Consolidation of the lung, usually bronchial or lobular in type, manifests itself at some time or other, sometimes early, but usually late. In the 20 cases reported by Klemperer, Pollack and Baehr, it was absent but twice. As we have already remarked, pneumonia is usually associated with a pleurisy with effusion. The pneumonia tends to migrate and may disappear and reappear a number of times before its lethal manifestation. Histologically, the pneumonic process is in no way distinctive (2).

O. *The heart exclusive of the pericardium.* Clinically, signs referable to the heart may be entirely absent throughout the course. Usually such signs arise in the intermediate or late phases. Tachycardia of considerable degree is the rule and is always noted terminally. Systolic murmurs may arise which cannot always be correlated with endocardial involvement, and contrariwise an endocarditis may be present without giving rise to a murmur. Gallop rhythm is common and usually a late event. Enlargement of the heart, if present, is usually moderate. The electrocardiogram shows no consistent pattern; the most common findings are low voltages and occasionally a prolonged P-R interval.

The main interest in Libman-Sacks disease centers around the endocardial involvement, which when present, is pathognomonic for this disease. In their original communication Libman and Sacks (10) emphasized the distinctive type of endocarditis at the expense of the clinical aspects, whereas, as a matter of fact, their clinical description of the disease which is remarkably complete, has since superseded the endocarditis in importance. Libman and Sacks employed the term "indeterminate verrucous endocarditis" since it had gross morphological characters distinguishable from the rheumatic and the bacterial varieties. Briefly, the vegetations are larger and flatter than those found in rheumatic fever and tend to spread for short distances along the valves or along the chordae tendinae. They appeared crinkled; the mural endocardium may be involved,

sometimes at a considerable distance from the valve; a favorite localization of the verrucae is in the angles between the flaps of the auriculoventricular valve and the mural endocardium. These were called "pocket lesions" by Gross. Histologically the most significant distinction from the lesions of rheumatic fever is the invariable absence of Aschoff bodies. The atypical verrucous endocarditis differs from bacterial endocarditis in a number of particulars. 1. Pericarditis is frequently associated with the indeterminate type but is excessively rare in bacterial endocarditis. 2. The vegetations are free from bacteria. 3. Blood cultures are invariably sterile. There are exceptions to these distinctions, both in respect to the rheumatic and to the bacterial type, as we shall discuss later. In their original communication, Libman and Sacks report four cases in which a full clinical picture of the disease which we have set forth is described, but they imply a distinction between the two cases in which a typical lupus erythematosus was present, and the remaining two in which it was absent. Strangely enough even in their report of these latter two cases, they described erythematous lesions on the extremities, one with purpura, which in the light of our present knowledge might have been regarded as true lupus erythematosus. This type of endocarditis is found in 30 per cent of all cases of disseminated lupus erythematosus. This figure applies only to the typical Libman-Sacks lesions. If one includes the cases previously described by Gross and Friedberg (29) Friedberg and Gross (30) and Friedberg, Gross and Wallach (31) as "non bacterial thrombotic endocarditis", with clinical histories closely resembling Libman-Sacks disease, some of which have since been shown (37) on further study to be genuine instances of the atypical verrucous endocarditis, the incidence would be higher. Furthermore, the percentage would again be raised if one included the early microscopic evidences of the beginnings of this type of endocarditis as described by Gross (32) and by Klemperer, Pollack and Baehr (2).

In their communication Libman and Sacks attempt to correlate this lesion not with the disease, but with the most striking sign of the disease, namely lupus erythematosus. This viewpoint has been perpetuated ever since, and has created confusion in regard to the proper nosology of the disease. As we have pointed out, lupus erythematosus need not be always regarded as an invariable accompaniment, nor have we the right to expect that it be so; even subacute bacterial endocarditis may pursue its course without petechiae, and scarlet fever may occur without a rash. Nor on the other hand have we a right to demand that the indeterminate type of endocarditis shall be an inevitable accompaniment of lupus erythematosus. A gross endocarditis does not always follow rheumatic fever. If one however, correlates the atypical verrucous endocarditis to the clinical picture, whether lupus is present or not, one is on surer ground, for I have not been able to find a single instance where an atypical verrucous endocarditis was found associated with some other type of malady than the one we have described. In other words, the lupus may be absent and the endocarditis may be absent, but the disease, whether complete or incomplete in its manifestations, is always present.

The Libman-Sacks disease cannot be defined with absolute certainty in all

cases by its clinical expression alone, because this is so often incomplete, but the diagnosis is absolute if the indeterminate verrucous endocarditis is found at post mortem. If this is absent and lupus erythematosus is absent, the clinical pathological diagnosis of Libman-Sacks disease can nevertheless be made with perfect assurance by finding one or the other of the visceral lesions that have been described so fully and accurately in the two contributions by Baehr, Klemperer and Schifrin (33) and by Klemperer, Pollack and Baehr (2). Viewing Libman-Sacks disease as a whole, the malady possesses well defined backgrounds clinically and anatomically and deserves a distinct place as a disease entity, and not as a syndrome.

The cardiovascular lesions in Libman-Sacks disease are further complicated by the not uncommon association with rheumatic endocarditis, bacterial endocarditis and the lesions of periarteritis nodosa. A rheumatic endocarditis was found in five of 23 hearts in Libman-Sacks disease, associated with the indeterminate type, which is a considerable percentage. Whether individuals with Libman-Sacks disease are more susceptible to rheumatic fever or vice versa awaits future study.

A bacterial vegetative endocarditis was found in four of the 20 cases reported by Klemperer, Pollack and Baehr. In one the staphylococcus was found in the blood culture; in the second a streptococcus hemolyticus; in the third, the streptococcus viridans, and in the fourth, an unidentified gram negative coccus. In one of three cases of Libman-Sacks disease reported by Keefer and Felty (34) a streptococcus viridans was found in a blood culture. In some instances, Klemperer, Pollack and Baehr could establish the fact that the bacterial infection was superimposed.

The lesions of periarteritis nodosa were found 3 times in the 20 cases reported by Klemperer, Pollack and Baehr. In a paper shortly to be published, (35) I tried to show that periarteritis nodosa is not a disease but a reaction conditioned by fibrinoid necrosis of the vessel wall. This accounts for its occasional occurrences in glomerulonephritis, in rheumatic fever and in the malignant phase of nephrosclerosis. In these disorders as well as in Libman-Sacks disease fibrinoid necrosis of the finer vessels is common. As Libman (24) states, there is therefore no purpose in attempting to make a clinical differentiation between Libman-Sacks disease and periarteritis nodosa. One is a disease in the true sense of the word, the other is only a complication which may have a number of clinical backgrounds.

Vascular lesions. The vascular lesions in Libman-Sacks disease are so frequent, so generalized and so pronounced that originally Klemperer, Pollack and Baehr regarded the disease as essentially a vascular one. Inasmuch as vascular lesions are absent in a small percentage of all cases, Klemperer, Pollack and Baehr in a later publication (36) now regard the disease as an affection of the collagen which they view as a tissue system comparable to reticuloendothelial structures. According to Klemperer, Pollack and Baehr, the vascular lesions are fairly generalized but they are found most frequently and in a severe from in the kidney. There is a considerable variation in the intensity and extent of

the vascular damage not only in the individual case but in comparison of case with case. The vascular lesions represent stages. The first change is a deposit of fibrinoid material within the intima, between the muscle fibres of the media or within the adventitia. Further progression leads to involvement of more and more of the vessel wall, the result of fusion of the fibrinoid material within these layers. With complete fibrinoid change of the collagenous framework, destruction of the muscular and elastic elements ensues. Complete occlusion of the vessel occurs by massive swelling. Despite extensive necrosis thrombus formation within the wall is exceptional.

The capillaries partake in this vascular change. These also are most pronounced in the kidney and consist in the "wire loop" effect of the glomerular capillaries or focal necrosis of these capillaries. Klemperer, Pollack and Baehr regard the necrosis as the end stage of the wire loop effect. These capillary glomerular changes were found in 17 of the 20 cases. In other organs one sees changes analogous to the wire loop lesions in the presence of fibrinoid rings replacing the basement membranes of the capillaries.

Is recovery possible? This is a difficult question to answer because the life cycle of the disease is a long one and it would require at least more than a decade of observation before a case is pronounced "cured." There are a considerable number of reported cases (13, 26, 12, 2) in which a lupus erythematosus disappeared for a period of between five and eleven years only to return and end fatally. In view of the necrotic nature of the vascular lesions, the productive lesions in the endocardium, the serous cavities and the joints, one would at best expect a clinical healing but not an anatomical one.

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Edgar D. Oppenheimer
May 10, 1883–April 29, 1946

Edgar was my friend. Indeed he was the friend of all of you who have come to pay respects to his fine personality. I have known Edgar for practically a life time. It is 40 years since we first met at The Mount Sinai Hospital on the house staff. Sweet and friendly as he was when I first came to know him, he never changed. His gentleness, kindliness and comradeship were charms of character possessed by few. His simplicity and modesty were so rare as not to be appreciated by those who were accustomed to more sophisticated personalities. But those of us who really knew him fully appreciated his utter selflessness, his intellectual honesty and total lack of sham. It can be truly said of him that he was never sullied by the material things of life. He never would compromise with the rules of ethical conduct. But while apparently betraying the simplicity of a child, he was possessed of the profoundest wisdom and emotional balance rarely encountered, even in one practicing his chosen profession.

Edgar was not a religious person in the ordinary sense of formal observance. Nevertheless, I am sure that every religious teacher would approve of the ethical principles which motivated his life. I have never known a more truly upright man. That is why we loved him and honored him, and shall now miss him. Of him it may be truly said that he never sought glory for himself, but that his whole soul was absorbed in serving those who came to him needing his skill—and his skill was great.

Although for the last five months he knew that he should not continue his labors at his accustomed pace, yet with utter disregard of self and with a smile upon his lips and the good humor which he never lost he continued to give of himself to the utmost. Only as recently as 10 days ago Edgar prepared and delivered a scientific address at the Academy of Medicine which embodied his basic philosophy of the practice of medicine as applied to his special field. He never ceased working to the last and when death overtook him he was engaged in the preparation of material for the next day's work.

In all his activities he showed the beauty of his character. The last ten years were occupied, in what leisure he could snatch, to cultivating the deeply native but dormant talent for painting. And how many of us here have found joy and pleasure in seeing the beautiful paintings he produced! The skillful hands which served him so well in his profession found an equal outlet in art.

We shall miss the skill of his hands, the wisdom of his mind, the warmth of his heart, his ready wit, the charm of his personality. We are grateful that we knew him. We shall not forget him.

We are consoled for his loss by the fine heritage he has left in the love of his friends, the hospitality of his home, the mutual devotion of his married life, and the fine principles he gave his boys.

Edgar D. Oppenheimer

Doctor Edgar D. Oppenheimer was born in New York City where he received his education first at The Sachs Collegiate Institute, then at Columbia University, receiving the A.B. degree in 1904. He entered the College of Physicians and Surgeons in 1903 and graduated in 1907. In July of that year he began his internship in the Mount Sinai Hospital and continued through November, 1908. He continued his post graduate training at Elizabeth General Hospital to January, 1910.

Having decided upon a career in orthopedic surgery, he entered the Charité in Berlin, January, 1910, and continued his studies abroad until May, 1911. Munich, Vienna, and other European Clinics were included in his visits until he returned to New York to take up the practice of orthopedics. When the first World War broke out, Doctor Oppenheimer joined the Mount Sinai Hospital Unit # 3 and was abroad for 14 months (1917–1918).

From the beginning of Doctor Oppenheimer's career as a specialist in orthopedic surgery he was associated with Mount Sinai Hospital both in the Out Patient and Ward Services, became Adjunct Orthopedist in 1918 and Associate Orthopedist in 1925. He left Mount Sinai Hospital in 1935 to become Attending Orthopedist at Beth Israel Hospital where he became Consulting in 1945.

Other Institutions where Doctor Oppenheimer was active, either in Consulting or in advisory capacities, were the Montefiore Hospital, Elizabeth General Hospital, The Bronx Hospital, Home for Hebrew Infants, Hebrew Orphan Asylum, New York Cancer Institute, and several others in which he gave his services free and in abundance.

He was a Fellow of the American College of Surgeons and the American Orthopedic Surgeons. He was on the Military Advisory Board from January, 1937 to the end of the second World War. He was a member of the American Board of Orthopedic Surgeons and also on the Advisory Board of American Orthopedic Surgeons. He also served as an impartial orthopedist on the Workmen's Compensation Board.

He was awarded a medal for work on the Medical Examining Board and Selective Service during the years 1942 to 1945. He was also the recipient of a number of medals for excellence in sports during his early college years and later for excellence in devising new apparatuses and gadgets which were adopted in his specialty. In his later years he developed an original concept in water color. To his surprise and delight it was given recognition at the Physician's Art Exhibitions. Doctor Oppenheimer made several significant contributions to medical literature, dealing with topics in his chosen field of surgery.

Eulogy delivered at funeral of Dr. Edgar D. Oppenheimer by Dr. I. C. Rubin at Temple Emanu-El, New York City, Wednesday, May 1, 1946.

ABSTRACTS

Authors' Abstracts of Papers Published Elsewhere by Members of the Mount Sinai Hospital Staff

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

Erythematous Lupus (Lupus Erythematosus). G. Baehr. Am. Heart Asso., 13:8, August, 1944.

In this article the following subjects are discussed: nomenclature, sex and age, etiology, pathology, clinical picture, and therapy. It is a concise and still complete review of the subject.

The Physiologic and Clinical Phenomena of Aging. E. P. Boas. New Orleans M. & S. J., 97:64, August, 1944.

This article can not be abstracted. It is brief and merits very careful reading. In this article the author describes some of the important phenomena of senescence and tries to distinguish them from disease in old age. Such knowledge is basic to scientific, clinical, and social study of our aging population.

Chart for Locating Common Causes of Breakdowns of Roentgenologic Equipment. C. B. Braestrup. Am. J. Roentgenol., 52:2, 227, August, 1944.

A chart was designed as a guide for roentgenologists and technicians in trouble shooting. It has been in use in the Department of Hospitals, New York City, for about two years and is based upon experiences with more than two hundred roentgen-ray machines of various makes and types.

Training and Healing after Apoplexy. W. G. Eliasberg. Clinical Medicine, 51:8, 203, August, 1944.

The general practitioner can do valuable work for his stricken patient if he cares to acquaint himself with what has been gained by the cooperation of neurologists, remedial pedagogues, and teachers in the institutions for the deaf, mute, blind, and feeble-minded. Last but not least, the psychologist and social psychologist have joined in such endeavors. The interested practitioner will also be called upon to cooperate in those greater organizational units that will have to take care of the brain injured victims of the war. Some personality type and psychological viewpoints are developed.

Influence of Vagus Stimulation on Nodal Rhythm. B. Kisch. Experimental Medicine & Surgery, 2: 259, August, 1944.

The effect of vagus stimulation on a heart beating in nodal rhythm is shown. The vagus effect slows the nodal rhythm, and can make it disappear entirely; the sinus rhythm returns during the vagus stimulation, and sometimes persists shortly afterwards. The return of the nodal rhythm is preceded often by a shortening of the P-R intervals (shifting pacemaker). The nodal rhythm in this case was produced by Strophanthin poisoning.

A Case of Digitalis Poisoning, with Morgagni-Adams-Stokes Syndrome. B. Kisch. Experimental Medicine & Surgery, 2: 262, August, 1944.

A case of digitalis poisoning in a 65-year old woman with coronary sclerosis is reported; the most apparent symptoms are very frequent attacks of Morgagni-Adams-Stokes syndrome, due to repeated a-v block periods, with ventricular standstills of 3–9 seconds dura-

tion. The EKG tracings show, in addition to these periods, nodal ectopic beats, a prolonged a-v conduction time, 2:1 block, and Q-R-S-T complexes of a prolonged duration (.66 sec) and a Wenckebach period of the sino-auricular conductivity. Each of the 15 recorded block periods starts with a dropped auricular beat—(sino-auricular block), and finishes as soon as an automatic (nodal) beat occurs, which restores the a-v conductivity. The path clearing effect of an ectopic beat on the a-v conduction, first proven in a human heart, is discussed in detail. The P waves show a definite Ta part. The marked Ta, as well as the depressed S-T in the EKG and the prolonged duration of Q-R-S-T and of P may be due to digitalis.

The Relation of Neurocirculatory Asthenia to Graves' Disease. E. Moschcowitz and S. S. Bernstein. Am. Heart J., 28: 177, August, 1944.

All evidences point to the psychosomatic nature of neurocirculatory asthenia. Neurocirculatory asthenia is by no means a disease incidental to war, and it is more common in women than men. Viewed from the dynamic and biologic aspects of Graves' syndrome, the similarity between neurocirculatory asthenia and the initial or larval phase of Graves' syndrome is so close that we believe the two are identical. Transitions of neurocirculatory asthenia to Graves' syndrome and the reverse are by no means uncommon. Eleven such instances are reported.

Industrial Radiation Hazards. C. B. Braestrup. Radiol., 43: 3, 286, September, 1944.

The results of this study indicate that a higher factor of safety and greater economy may be obtained in planning industrial x-ray protection on the basis of all the factors involved instead of simply the tube voltage, as has been the general practice in the past. Such determinations have been simplified by charts provided for the usual range of voltage, milliampere-minutes, and distance. Industrial radiation injuries are not necessarily eliminated by adequate structural shielding and safe equipment. Of equal importance are the training and practice of the technicians in safe operating procedures and their understanding of the fundamental technical and clinical aspects of protection, which not only reduces radiation hazards but also eliminates unfounded worries, so frequently caused by misinformation.

Psychogenic Incontinence of Feces (Encopresis) in Children. Report of Recovery of Four Patients Following Psychotherapy. E. Hehman. Am. J. Dis. Child., 68: 19, September, 1944.

Encopresis has been defined as "the act of involuntary defecation which is not directly due to organic illness." Anyone who carefully studies children with this symptom must conclude that this disorder is of psychic origin. Often the fundamental cause is lack of parental love for the child. This is true in cases due to sibling jealousy after the birth of a younger child, or where the home is broken as with orphans and foster children. The child with encopresis may live in an unhappy home, for example, where the mother is extremely domineering or where the father institutes an educational regime that is calculated to develop an infant prodigy. Frequently this disorder is a reaction against scholastic authority. In some cases the mother is excessively preoccupied with the child's intestinal functions. Anxiety may be an important factor as in cases of involuntary defecation precipitated by present war conditions. Encopresis can be directly caused by a toilet phobia or less directly by the anxiety of other phobias unrelated to defecation. In a girl of six the soiling was caused by abnormal fear of fire engines and the air raid siren, and the phobia of this child resulted from witnessing the parents in coitus before the age of three. To avert such psychic trauma no child should sleep in the parents' bedroom. Children with encopresis may exhibit not only aggressive and sadistic attitudes but also marked masochistic trends. Another psychic mechanism sometimes involved is regression, which is exemplified in the case where, due to sibling jealousy, a girl of seven had a definite unconscious fantasy of being a baby again. Involuntary defecation is normal in early infancy,

and if a child has never been clean, it may be due to lack of training. Encopresis is more frequent in the feebleminded, but the same psychic factors may operate in the mentally defective as in the normal child. In one type of encopresis (obstipatio paradoxa) there is not only incontinence of feces but also marked obstipation, resulting in an enlarged abdomen containing palpable fecal masses, a rectum overdistended with hard feces, and usually a perianal dermatitis. The child's unconscious ideas about the feces produce this syndrome. The therapeutic approach recommended is based upon psychoanalytic insight and methods, since these have in practice been most productive of lasting results.

Dermatophytosis in Industry. S. N. Peck, I. Botvinick and L. Schwartz. Arch. Dermat. & Syph., 50: 170, September, 1944.

A group of 2,123 workers were examined for fungous infections of the hands and feet. In this group there were 1,393 men and 730 women. On clinical grounds alone results for the 2,123 workers were classified as follows: 27.79 per cent positive, 33.63 per cent doubtful and 38.57 per cent negative. It was shown by cultural studies that some patients in the clinically doubtful group had true dermatophytosis. There was no significant difference in sex incidence. When the personnel of the same plants was examined at different seasons, the number of clinically negative workers rose from 13 to 19 per cent in the summer to 54 per cent in the winter. T. gypseum was the pathogenic fungus most often recovered, T. purpureum was next in frequency and inguinale was recovered from 1 case. All of the cultures of T. purpureum were recovered in one locality. Shower room flooring of concrete or pine wood is a possible but not likely source of fungous infections of the feet. A type of copper-impregnated concrete flooring was found to be of no value in the prevention of the spread of fungous infections of the feet as far as could be determined with the experimental procedures used. Trichophytin tests were made on 776 workers. Of this number 42.53 per cent had positive reactions, and reactions of 57.47 per cent were negative. Of the 558 men tested, 52 per cent had positive trichophytin tests, and 48 per cent negative; of 218 women tested, 29.96 per cent had positive trichophytin tests and 70.04 per cent negative. The lower incidence in women of a demonstrable allergy to fungi and/or their products may offer an explanation for the belief that women are less affected by dermatophytosis of the feet than are men, since it may be responsible for less subjective symptoms. The trichophytin test is more often positive in patients with clinically active dermatophytosis of the feet than in those showing no evidence of the disease. There is no indication that the presence of an allergy to fungi and/or their products bears any relationship to the acquisition of an allergic contact dermatitis. Dermatophytosis and its allergic manifestations have not been found to be an important factor in lost time among industrial workers.

The Peckham Experiment. G. Baehr. Milbank Memorial Fund Quarterly, 22: 352, October, 1944.

This is a description of the pioneer health center in London which was established in 1926 through the thoughtful planning of a group of persons under the leadership of Dr. G. Scott Williamson and Dr. Innes Pearse. The Peckham Experiment was indeed a study of the living structure of society by physicians trained in social medicine and human biology. A project of this kind could not fail to influence the many medical, environmental, hereditary, and social factors responsible for disease and dependency, and upon that all embracing condition called social poverty, the elements of which are to be found among all classes, but especially among people in the low economic levels.

Disorders of Male Sexuality as Encountered in the Practitioner's Office. W. G. Eliasberg. Psychiatric Quarterly, 18: 1, October, 1944.

While there can be no doubt that personality factors, psychological makeup, acute factors of the psychological situation play an overwhelming rôle in the syndrome of male impotence, these factors themselves are of an astonishing variety. The psychosexual

condition of each case must be analyzed in itself. Only after an analysis of the psychological situation, which need not always be a psychoanalysis, can one gain insight into the dovetailing of the physical stigmata, if any, with the psychological makeup. The treatment should never begin before such analysis. The treatment will consist of a psychological and endocrine-autonomic part. Other cases may also require nutritional and local neurological armamentaria. But these latter are relatively rare cases in the physician's office. The psychoneurotic type which is least connected with and gives the strongest protection against impotence is conversion hysteria. On the other hand, the impotence syndrome shows an affinity for the schizothymic split personality type with or without the autonomic imbalance syndrome.

Graphology and Medicine. W. G. Eliasberg. J. Nerv. & Ment. Dis., 100: 4, 381, October, 1944.

True graphology rests on the fact that there is psychophysical correspondence and particularly a motor and spatial symbolism corresponding to the emotions and character traits. Both character graphology and a knowledge of handwriting are indebted to medical pathology. Graphology, like psychology, while keeping abreast of the developments in neighboring sciences, among them neurology is, however, an independent science and must be developed as such, not as a handmaiden of neurology, but as an equal partner. The most valuable contribution of neurology and physiology to graphology consists in the clarification of the physiological process of writing. Future development will have to show to what degree phsyciological, psychological, and sociological factors may influence the individual handwriting. At present we may say that the so-called emotional psychoses may cause sociological factors to disappear while they may combine in handwriting and in the mind with various psychological factors. Future experimental work will have to compare our present graphological convictions with the graphs gained through one of the modern methods of expressive psychology. Laymen cannot diagnose diseases. They should not do it under the guise of graphology either. Medicine may use graphology for a) diagnosis of disease entities and differential diagnosis, b) the prognosis of the development of the disease and for the prognosis based on the character of the patient; c) better knowledge of the subjective factors, among them the adjustment of the patient to his disease; d) records showing the course of the disease and the effect of treatment; e) for better use of the psychological factors in treatment; f) special applications; (1) for psychological evaluations according to the above-listed prognosis of life-insurance prospects, (2) evaluation of the subjective and the physiological age of the writer as compared with his chronological age. Two sub-branches of graphology will gain importance: a) development of graphology comparing the different stages of maturation and individual development; b) pathographology, comparing the pre-morbid, morbid, and post-morbid handwriting of the same individual. This can also be used for groups and for inter-group and international comparisons. Understanding of the handwriting of ruling elites is an important contribution of political graphology.

Causes of Mortality following Radical Resection of Esophagus for Carcinoma. J. H. Garlock. J. Thoracic Surg., 13: 5, October, 1944.

The author makes a careful analysis of 131 cases of the esophagus and cardia. Of this group 60 were found operable and treated by radical surgery. In this analysis special attention was paid to the causes of operative deaths. In the majority of these, postmortem examinations were carried out. Deaths were classified under 2 headings: 1. due to preventable causes and 2. due to factors beyond the control of the surgeon. Cardiovascular accidents, such as coronary thrombosis, cerebral accidents, pulmonary embolus, heart failure etc. accounted for 15 deaths. 6 patients died of overwhelming pneumonias. The author also reports that 17 patients are alive and doing well for periods ranging between 8 years and 1 month.

Primary Sarcomatous Meningioma. J. H. Globus, S. Levin and J. G. Sheps. J. Neuropath. & Exper. Neurol., 3: 311, October, 1944.

Of 150 meningeomas (from the Neuropathology Laboratory of the Mount Sinai Hospital) surveyed, 16 or 9.3 per cent were sarcomatous. Such tumors are often wrongly diagnosed because of failure to employ all of the available diagnostic staining methods and because the presence of glia cells (responding to the invading mesodermal derivatives) is often overemphasised and misinterpreted. Eight cases are reported in full and a summary of the clinical features and anatomical findings is presented. Two of the eight cases had multiple lesions and diffuse sarcomatosis of the meninges. The sarcomatous meningeomas are found to have the characteristics of sarcomata elsewhere (including the ability to yield visceral metastases). Their origin can be traced to derivatives of the pial component of the meninges and in general the cells exhibit a recession in the process of differentiation. A classification of meningeomas, based on the phylogenic concept of Globus, is recapitulated. Sarcomatous meningeoma cells are readily identified with the vascular derivatives of the mesenchymal mass which forms the meninges. The nature of the tumor explains its failure to respond well to surgical intervention but does not explain why x-ray is of so little aid.

The Measurement of Electric Potential in the Stomach. F. Hollander. Gastroenterol., 3: 319, October, 1944.

The work of several investigators on intra-gastric potential, the method of its measurement, and its value as a diagnostic tool in detecting gastric ulcer and carcinoma, is summarized in the present review. The validity of variations in the electrical pattern as a diagnostic criterion has been questioned by subsequent workers, and this uncertainty has been traced to uncontrolled liquid-liquid junction potentials. It is suggested that further work be done to modify the present techniques so that a knowledge of the correct basic gastric potential may be acquired, even though clinically observed deviations from this value may prove to have little or no diagnostic value. A procedure is outlined for supplying accurate records of the pH of stomach contents *in vivo*.

Bicipital Tenosynovitis. K. Lippmann. New York State J. Med., 44: 20, October, 1944.

The typical clinical aspects of periarthritis, or frozen shoulder, are reviewed, with emphasis on the fact that, though its duration is unpredictable, the condition almost invariably terminates spontaneously in complete recovery. Surgical investigation of more than 30 cases of frozen shoulder has revealed that at least in most instances the subdeltoid bursa and underlying musculotendinous cuff are not involved and that, instead, tenosynovitis of the long biceps tendon and sheath is consistently encountered. Adhesive tenosynovitis extends from the sheath into the outer quadrant of the shoulder joint proper, but the entire inflammatory process subsides spontaneously when the tendon becomes firmlyattached to the bicipital groove and its motion is so obliterated. The pathologic sequence underlying periarthritis provides a guide for the administration of conservative therapy and suggests a simple surgical approach when more rapid cure is desired.

The Problem of Embolism of the Pulmonary Artery. H. Neuhof. Ann. Surg., 120: 488, October, 1944.

An operative procedure is described which is simple, reasonably safe, and does not require undue haste. Special skill and practice and a special team are not needed. The suction of blood, which results in some measure of decompression of a right ventricle laboring unavailingly against the obstructing embolus, is a desirable feature. However, the essential part of the operation is performed blindly and does not provide assurance that suction will, in fact, engage the thrombus in the eye of the catheter. A metal tube with an appropriately hollowed end would probably be more effective in engaging and extracting the thrombus. Despite the fatal issue in the reported case, further attempts to extract a pulmonary embolus through the right ventricle appear justified.

Surgical Jejunostomy for Alimentation. A Historical Review. S. Rosenak and F. Hollander. Clinics, 3: 638, October, 1944.

This review with complete bibliography presents the history of jejunal feeding and surgical jejunostomy from 1858. The first jejunostomies were performed in France and England, solely as emergency operations. This method of feeding was abandoned repeatedly, however, because of (1) inadequacy of surgical techniques, and post-operative complications; (2) inadequacies of the food used, resulting in jejunitis and improper utilization; (3) inadequacies of the technic of administration, causing overloading of the small bowel with consequent distention, nausea, vomiting, pain, and diarrhea.

As to (1), the first practical and usable technic for surgical jejunostomy was devised by Maydl in 1888, and followed the pattern of the Wolfler-Roux "Y" gastro-entero-anastomosis. When successful, it was used mostly for permanent intestinal feeding, but it entailed a considerable operative mortality. More successful was the technic of Eiselsberg (1895), which was based on Witzel's gastrostomy, and that of Helferich (1904), which became known later as the Coffey technic. The most practical and rapid method for the establishment of a temporary jejunostomy is that of Stamm and Hofmeister, which is used by most surgeons at present and is considered by Colp and Druckerman to be the safest.

Concerning (2), the aliment in the past has always been a mixture of common food-stuffs. Besides suffering from cramps, vomiting, and diarrhea, most patients couldn't be maintained in nutritional equilibrium on such mixtures, and they continued to lose weight during enteric alimentation. The pabulum introduced by Scott and Ivy improved the results of feeding somewhat, but it also caused cramps and diarrhea in about 10 per cent of the cases. The need for a bland and predigested feeding mixture specially adopted for these purposes was satisfied by the formula developed by Hollander, Rosenak and Colp. Their aliment is well balanced, high in predigested protein (enzymatic digest of casein) and carbohydrate (a mixture of dextrin and maltose), low in fat and contains adequate amounts of mineral salts and vitamins. In order to compensate for disturbances in water and acid-base balance, the sodium chloride content is well above the normal requirement. This mixture is utilized adequately and it seems to be well tolerated by the patients fed on it exclusively.

As to (3), the mass injection method which was prevalent in the past has been superseded by the drip feeding, as first recommended by Kelling. It has been recommended also that the temperature of the feeding mixture, but especially a predigested one, should be sterilized to prevent bacterial growth and the development of toxins.

Enhanced Production of Penicillin in Fluid Medium Containing Cellophane. G. Shwartzman. Science, 100: 390, October, 1944.

Enhanced production of penicillin is made possible by addition of Cellophane to fluid media. With Cellophane bags of suitable surface, the growth of the submerged and surface penicillin producing strains of *Penicillium notatum* is significantly faster and more abundant; penicillin makes its appearance earlier and reaches higher concentration in larger total volumes than in control cultures without Cellophane*. Thus the gain with the method described is both in the rate of production as well as in the total yield of penicillin. The enhancement also occurs under conditions unfavorable for development of penicillin, namely (a) with degenerated cultures of the mold; and (b) when the surface penicillin producing strain is grown in cultures with an unfavorably small $\frac{\text{surface area}}{\text{total volume}}$ ratio (0.0315). There is also noted a markedly stabilizing effect of Cellophane upon the H-ion concentration of abundantly growing cultures during active production of penicillin. The stabilization is of significance, since the sharp rise in pH usually occurring in Penicillium cultures tends to destroy rapidly the penicillin.

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* In subsequent experiments in which large numbers of Cellophane strips instead of the bags were used, there was obtained markedly greater and faster production of penicillin than described in this report.

Some Characteristics of Mucus Secretion in the Digestive Tract. F. Hollander. Gastroenterology, 3: 403, November, 1944.

This report summarizes the results of four years of work on the chemistry and microscopic appearance of mucus secretion in the dog's stomach, and is based on the study of large groups of data. The pH of this secretion, obtained with various chemical stimuli applied topically, falls between 8 and 9; lower values are due to the admixture of transudate and exudate. Chloride concentrations varied between 57 and 186 mN. Buffer capacity (i.e., acid-neutralizing power) between the initial pH and 3.5 range as high as 84 mN. Correlation coefficients of pH with these other variates are −.4 and 0 respectively. These results demonstrate that native mucus has the potentiality of neutralizing HCl intragastrically, but the volumes ordinarily secreted may not be large enough to be significant in this respect. Smears of this secretion were stained with Wright's and with Toluidine Blue, the latter by a technique for permanent metachromatic staining previously reported. Transparent mucus (jelly or viscous fluid) is obtained sometimes as a spontaneous secretion, and always by stimulation with 1% mustard oil emulsion; the material obtained with other chemical irritants (e.g., alcohol, water saturated with ether, and clove oil emulsion) is invariably opaque. The opacity results from the presence of columnar cells—singly, in ranks, or in clumps; also from goblet-like cells, lymphocytes, and leukocytes. The mucin *per se* is sometimes vacuolated, and sometimes it contains various types of crystal formations. Conclusions regarding the significance of these observations are left for the final, detailed reports.

Presystolic Murmur without Auricular Systole. A Clue to the Genesis of Auricular Sounds. F. M. Groedel and B. Kisch. Experimental Medicine & Surgery, 2: 319, November, 1944.

Five cases, each with auricular fibrillation or flutter, in whom a presystolic murmur was clinically proven, are reported. In one (a mitral stenosis) phonocardiograms were taken both during a period of regular sinus rhythm as well as one of auricular fibrillation. These observations prove that a regular auricular systole is not necessary to produce a presystolic murmur.

Transient Intraventricular Conduction Defect. B. Kisch and A. Grishman. Experimental Medicine & Surgery, 2: 277, November, 1944.

Four different mechanisms producing transient intraventricular conduction defect have been demonstrated and discussed. 1. Cardiac alternation due to an alternating intraventricular conduction defect. 2. Transient intraventricular conduction defect due to vagal stimulation. 3. Transient intraventricular conduction defect due to quinidine and digitalis. 4. Transient intraventricular conduction defect due to tachycardia (shortened R-R interval) in coronary insufficiency.

Antipressor Effect of 1,4 Cyclohexandione on the Blood Pressure of Hypertensive Dogs. B. S. Oppenheimer, B. E. Lowenstein and C. Hyman. Proc. Soc. Exper. Biol. & Med., 57: 117, November, 1944.

It has been shown by various authors that some of the quinones are effective as antipressor agents in hypertensive rats and hypertensive dogs. It was found by the authors that some of the compounds were extremely toxic when used on dogs. A search was made for related compounds which had antipressor effects and still had a low or no toxicity. A diketone, 1,4 Cyclohexandione when administered intramuscularly to 7 different hypertensive dogs, seemed to reduce the blood pressure by an average of 30 mm. of Hg, and yet in the dosage employed resulted in no local or general toxic effects. The experiments are being continued.

Ovarian Fibromas and Theca Cell Tumors. Report of 78 Cases with Special Reference to Production of Ascites and Hydrothorax (Meig's Syndrome). I. C. Rubin, J. Novak and J. J. Squires. Am. J. Obst. & Gynec., 48: 601, November, 1944.

The report is concerned with an analysis of 53 cases of ovarian fibroma, 2 cases of papillary fibroadenoma and 23 cases of theca cell tumor. The analysis has led the authors to the conclusion that contrary to many statements in the literature, ascites does not frequently occur in ovarian fibromas if all sizes of this type tumor including the small ones are considered. The combination of ascites and hydrothorax (Meig's syndrome) was found only in one of their cases of ovarian fibroma and in one case of theca cell tumor. The ascitic fluid is apparently a transudate originating in all probability from the tumor itself. It is transferred from the peritoneal into the pleural cavity by diaphragmatic lymph channels which are described in detail. Living cells, cell debris or chronic inflammatory changes of the peritoneum or of the pleura, may block the connection between these two cavities. Animal experiments in which the authors tried to reproduce similar conditions appeared to corroborate these assumptions. The greater incidence of right-sided pleural effusions can be explained by the better development of lymph channels in the right half of the diaphragm, the higher position of the right diaphragmatic dome and by its more powerful pumping action, all of which tend to transfer the ascitic fluid to the right pleura.

Inhibition of E. Coli by Penicillin. G. Shwartzman. Science, 100: 477, November, 1944.

Within a certain range, there exists a linear relationship between the log of E. coli cells at zero hours and the concentration of penicillin in O. U. per ml. required to produce complete inhibition. Methionine inhibits the growth of E. coli. Methionine and penicillin exert together a synergistic inhibitory effect upon the microorganism. Inhibition of growth obtained with a mixture of rabbit blood serum and penicillin may exceed somewhat the sum of inhibition induced by each ingredient, separately. The inhibitory effect of methionine alone may be abolished in considerable part by blood serum. "Neutralized" mixtures of methionine and serum producing by themselves only incomplete inhibition may greatly increase the susceptibility of E. coli to penicillin.

The Value of Roentgenologic Examination of the Heart. M. L. Sussman and A. Grishman. Am. Heart J., 28: 5, 647, November, 1944.

It is generally realized at the present time that roentgenologic examination of an organ in most instances is only part of the clinical examination. This is true particularly of roentgenologic examination of the heart. The current criteria for the roentgenologic diagnosis of heart disease are based often upon physiologic reconstructions which do not occur as simply in practice. Certain important modifications have been suggested as the result of angiocardiographic study. There is no reason to use a method beyond its proper limits to extract information which is of questionable accuracy and which can be obtained more easily by other means. Hence, it is when the roentgenologic observations are considered critically as part of other clinical data that the examination is of real value. Alone, it may be insignificant or ev misleading.

Exit Dose in Dermatologic Roentgen Therapy. C. B. Braestrup, Andrews, G. C., and Heisel, E. B. Arch. Dermat. & Syph., 50: 355, December, 1944.

The exit dose and skin dose were measured on both hands of 40 persons and on both feet of 12 persons. The quantity of radiation received by the alae nasi in the treatment of acne vulgaris was determined. When both surfaces of the hand are irradiated, the exit dose and back scatter increase the skin dose over the air dose to each surface of the hand by the following average percentages: 25 per cent with radiation produced at 65 kv, 45 per cent at 100 kv and 78 per cent when the radiation is produced at 135 kv with a 3 mm. Al. filter. These percentages may be applied in practice to any air dose given to both surfaces of the average hand. While there will be variations due to differences in thickness, these are generally too small to require correction.

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TOPICS IN THE STUDY OF WATER-METABOLISM*

ERNEST P. PICK, M.D.

The purpose of this address is to give you a short, and therefore necessarily incomplete, survey of recent experiments concerning some diuretics and antidiuretics produced by the endocrine glands, and to draw your attention to some still unsolved problems. I shall not speak in detail about the well known functions of the kidneys as regulators of water and electrolyte metabolism. It is fully understood that kidney tissue is indispensable for the maintenance of water, electrolyte, acid and alkaline balance in the blood and tissues. This is well demonstrated by measurement of urea in the blood and urine which shows that of the more than 600 liters of blood which pass through the kidneys in 24 hours about 50 liters of fluid are filtered out by the glomeruli and 48 liters are reabsorbed (1). According to the creatinine and insulin clearance tests of Smith (3) and Rehberg (2), from 125 to 200 cc. of fluid, respectively, will be filtered through the glomeruli in one minute; that is, 200 to 288 liters in 24 hours, of which 99 per cent are reabsorbed. In addition to this most important regulating function of the kidneys, several endocrine glands and tissues possess the ability to alter the water and electrolyte balance between blood and tissue fluid, thereby definitely changing urine secretion. I shall consider the hormones of the *pituitary*, the *thyroid*, the *adrenal cortex*, and the *liver*, and discuss clinically observed and experimentally produced deficiencies of these hormones.

I. THE PITUITARY AND DIABETES INSIPIDUS

Involvement of the *pars nervosa* of the hypophysis in the production of diabetes insipidus was first demonstrated by Frank in 1910 (4). Three years later van der Velden (5) showed that injection of extracts of the posterior lobe of the hypophysis markedly decreased the polyuria in cases of diabetes insipidus. A better understanding of the disease was first brought about by Camus and Roussy (6), when they demonstrated, in 1913, that a lesion restricted to the hypothalamus produces diabetes insipidus. Verney (7), in 1936, expressed the view that normal water diuresis depends upon the integrity of the pars nervosa of the pituitary, and that its loss should lead to maximum diuresis. This hypothesis was supported by the most careful experimental work of Fisher, Ingram and Ranson (8). Using the Horsley-Clarke stereotaxic instrument for the production of well circumscribed experimental brain lesions they showed, in 1938, that the *pars nervosa and the supra-optic nuclei and tracts* must be considered as a single functional unit, which is able within certain limits, to regulate the body's water and electrolyte metabolism. Interruption of the hypothalamic tract connecting the paraventricular supra-optic nuclei with the pars nervosa of the hypophysis

* Lecture given in the Seminar of the Department of Pharmacology, School of Medicine, Yale University, February 21, 1946.

produces grave disturbance of the water-electrolyte metabolism and diabetes insipidus. Therefore, Ranson's conception of the anatomical implication in diabetes insipidus is that the hypothalamus regulates the secretory activity of the pars nervosa through the supra-optico-hypophyseal system; and also, as did von Hann (9), he implies that normal water metabolism is maintained through an antagonism between the posterior and anterior lobes of the hypophysis. The latter concept was based on the observation that diabetes insipidus occurs clinically only if the posterior lobe is destroyed while the anterior lobe with its diuretic influence remains intact (9a). Alongside of this hypothesis there was a general agreement that, as suggested by Verney and collaborators (10), the sensitivity of man and dog to the antidiuretic actions of the pituitary is inversely proportional to the water-load of the organism, in other words, the need for water conservation by the body acts as a stimulus to posterior pituitary secretion.

The whole problem received a new impetus from the observation of Gilman and Goodman (11) that infusion of hypertonic saline greatly increases urinary excretion of so-called pituitrin, while hypotonic saline or 5 per cent glucose solution or pure water inhibits the elimination of pituitrin through the urine. Urine of the hypophysectomized rats contains no antidiuretic substances, and even cats with diabetes insipidus due to interruption of the supra-optico-hypophyseal tract without direct injury to the hypophysis, do not excrete antidiuretic substances even when dehydrated (12). It has been postulated, therefore, that for the regulation of the water and salt exchange there is a hypothalamico-hypophyseal mechanism: the latter controls the secretion of pituitrin through its sensitivity to changes in the salt content of the blood and thereby controls the concentration in which salt is absorbed in the renal tubules. Chambers and co-workers (13) substantiated this concept by determining that the intravenous administration of solutions which elevate the osmotic pressure of the plasma cause an increase in the secretion of pituitrin. The renal tubules respond to the increased amount of pituitrin in circulation by reabsorbing from the glomerular filtrate a solution with an osmotic pressure less than that of the plasma. Solutions which *lower* the osmotic pressure of the plasma produce the opposite effect in that they inhibit the release of pituitrin.

Such a release of pituitrin with consequent inhibition of water diuresis is enhanced by various stimuli. Among them is emotional stress as was first demonstrated on dogs and rabbits by Molitor (14) and later by Verney and associates (15). They showed that the antidiuretic action may be complexly determined and the result of sympathetic stimuli as well as the release of pituitrin: an interruption of the splanchnic nerves, denervation of the kidneys and suprarenals abolish the *rapid* inhibition, while transsection of the hypothalamico-hypophyseal tract abolishes the *slow* inhibition. Even antidiuretic actions by morphine [Bonsmann (16)] and by barbiturates, which depress the activity of the hypothalamus [Pick (17), Molitor and Pick (18)] according to de Bodo (19) may also be due to the action of the neurohypophysis in dogs. The destruction of this structure in dogs resulted in permanent diabetes insipidus, but the use of barbiturates and morphine never inhibited the excretion of water, indicating that the hypothalamic region is the probable site of action of these drugs. The findings are in

accord with the older observations of Mehes and Molitor (20) on rabbits and dogs with experimental lesions in the hypothalamic region, which no longer responded to the diuresis inhibiting action of posterior pituitary extracts. In this connection the striking observation of Chen, Oldham and Geiling (21), that the response to the posterior pituitary extract of hypophysectomized frogs or frogs with a lesion in the floor of the third ventricle decreases very sharply, is worth mentioning. This seems to indicate that the mode and site of action of posterior pituitary extract in these animals, depends on the integrity of the floor of the third ventricle.

As yet, no sufficient evidence is available for the ingenious hypothesis that the hypothalamico-supra-optic-hypophysis pathway system is the efferent limb of a reflex arc which may be activated by stimulation of somatic afferent fibres [Chambers and co-workers (13)] and thus increase the rate of pituitrin secretion and regulate entirely the water and electrolyte balance. The physiological mechanism for the release of an antidiuretic hormone from the neurohypophysis is not yet identified nor were these antidiuretics chemically isolated or pharmacologically characterized. Moreover, it should be borne in mind that Heller and Urban (22) have demonstrated the rapid disappearance of the antidiuretic pituitary principle from the circulating blood after intravenous injection of posterior pituitary extracts; half of the injected amount may be absorbed by the blood proteins, the rest inactivated in the tissues, especially in the liver. Only very small amounts are excreted in the urine. This is also true in rabbits and dogs (23). Still more doubtful is the urinary excretion of an antidiuretic substance after subcutaneous injections of posterior pituitary extracts into rats [A. M. Walker (24)]. Moreover, the entire aforementioned concept is considerably weakened by the findings of Smirk and Newton (25), who observed that the anterior pituitary body is not absolutely indispensable for the production of water diuresis; they claim to have obtained the typical response in animals after removal of the entire pituitary, hypothalamus and all brain tissue above the tentorium cerebelli. Recent results of experiments by M. Pickford and A. E. Ritchie (26) point in the same direction, showing in dogs the gradual disappearance of polyuria after destroying the hypothalamic-hypophyseal system even after removal of the anterior lobe of the hypophysis. It may be also mentioned that completely hypophysectomized rats are, as Chen and Geiling (27) emphasize, not suitable for the estimation of the antidiuretic principle of the posterior hypophysis because these animals respond to the antidiuretic principle of the posterior pituitary extract as do normal animals. Such observations indicate an establishment of a new water and electrolyte balance and suggest that other processes slowly become efficient in controlling the volume of water retained in the body. The diuretic and antidiuretic hormones of the hypophysis are beyond doubt only a part of the extrarenal water and salt regulating factors and there are certainly other hormones to be considered as factors in the maintenance of water and salt balance.

II. THYROID

The action of thyroid on the water metabolism has been known for nearly 50 years since Magnus-Levy (28) described in 1897 the loss of protein, fat, water, and

increased urinary nitrogen excretion in hyperthyroidism. The diuretic action of thyroid was recognized first by Coronedi (29) and later studied by many authors (30, 31). There still remain many unsolved problems concerning several aspects of the diuretic action of the thyroid, particularly its relation to the diuretic function of the anterior lobe of the hypophysis. It is known that the administration of thyroid exaggerates polyuria in animals with diabetes insipidus, while thyroidectomy reduces the urinary output (32). Cats as well as dogs are so affected. Diuresis induced in rabbits by thyroxin can be easily inhibited by very small amounts of posterior pituitary extracts (31). Lichtwitz (33), moreover, reports a case of Strauss in which diabetes insipidus disappeared after development of myxedema and mentions the observation of T. Findley that thyroidectomy increases the effect of pitressin. "These observations have led to an attempt to control diabetes insipidus by thyroidectomy, with good results reported in a few cases." However, the diuretic effect of thyroid is not altogether clear because in the absence of the anterior lobe (which produces the thyrotrophic hormone) thyroid feeding does not produce any polyuria in dogs. Ingram and Fisher (34) could not suppress the diabetes insipidus by thyroidectomy in cats, and White (35) was unable to produce diuresis in hypophysectomized rats by administration of either anterior lobe extract or of a combination of anterior lobe and thyroid extracts. It is assumed that the diuretic effects of thyroid in rats depends upon the presence of the anterior pituitary and hypertrophy of the adrenal cortex; adrenalectomy abolishes the increased diuretic effect of hyperthyroidism. Of interest is the fact that in thyroidectomized guinea pigs made exophthalmic by extracts of the anterior pituitary gland, the hypertrophy of the orbital fat tissue and the extraocular muscles were found to be due to an increase in total water content rather than to an increase in fat [Smelser (36)]. The diuretic effect of the thyroid in humans is sometimes of therapeutic importance since the thyroid appears to increase the glomerular filtrate. Thus, in mercurial poisoning and other cases of renal insufficiency the damaged kidney output is considerably improved by the administration of thyroid (30).

Final mention should be made of the generally known fact that the myxedematous swelling in hypothyroidism is, according to Boothby (37), due to an increase in the quantity of protein deposit which holds in association, or absorbs large amounts of water. Under the influence of thyroidin or thyroxin there occurs a breakdown of protein colloids with the liberation and elimination of water.

III. ADRENAL CORTEX

Another example of endocrine gland secretions which effectively regulate water and salt metabolism is found in the suprarenals; the possibility exists that even these glands are directly or indirectly influenced in this function by the pituitary gland. According to Kendall (38) desoxycorticosterone and the residual amorphous fractions remaining after the removal of crystalline products from cortex extracts are highly potent (2 μg. per Kg) in maintaining salt and water metabolism, renal function, capillary permeability and, above all, life. Even the lag in

water excretion which occurs in hypophysectomized dogs can be prevented by administration of adrenal cortex hormones. This strongly suggests an adrenocortical control of water metabolism in the organism. On the other hand, Loeb, Harrop, Swingle and their associates (39) have shown that adrenal cortex insufficiency appears to produce increased elimination of sodium chloride by the kidneys and retention of potassium and water in the cells. There appears a cellular hydration and also an anhydremia as shown by the low blood volume and the high hemoglobin and serum protein concentration. Adrenalectomized mice, dogs and rats show a markedly reduced diuretic response to administration of excessive amounts of water and a greatly increased susceptibility to water intoxication with generalized weakness and convulsions. Adrenal gland deficiency has been found to cause a marked retention of water: after receiving 20 cc. of water per 100 gm. of body weight, adrenalectomized rats retain 12 cc. as compared with 2 cc. for a normal group. Desoxycorticosterone exerts a protective effect against water intoxication in normal animals and abolishes the increased susceptibility of adrenalectomized animals (40, 41).

A striking alteration in water and salt metabolism is shown by the patients in Addison's disease. In such patients, rapid injection of large amounts of water is not followed by an increase of the excretion of urine, even when water is administered intravenously in the form of 5 per cent glucose solution or of physiologic saline solution. This reduction of the concentration of plasma electrolytes does not act as an effective diuretic stimulus, and the patient still fails to secrete urine at normal rates (42).

Another very important phenomenon is the inability of these patients to regulate the losses of sodium chloride by maintaining normal storage. When a normal animal or human is deprived of sodium chloride, total excretion of sodium is markedly reduced. The normal organism possesses great capacity to maintain the sodium chloride content of its cells and extracellular fluids on a constant level. The tissues carry on normal functions when sodium chloride must be conserved and the "*liquid milieu interieur*" remains unchanged even when urine highly concentrated in sodium chloride is excreted. The Addison patient, however, when deprived of sodium chloride is unable to maintain the necessary salt level of the tissue fluids. The urinary concentration of sodium chloride remains high, relatively constant and fixed, the blood is depleted of its saline, the blood volume is reduced and the patient "goes into a crisis." The potassium level is raised to within toxic ranges. These subjects lose the capacity to concentrate urine under conditions of water restriction, and to dilute urine under condition of water plethora. Only the administration of suitable amounts of sodium chloride (10–20 gm. daily) together with sodium citrate and sodium bicarbonate improves the condition of the patient and allows decrease of the dose of cortical extracts (42). At the same time the amount of potassium in the diet must be reduced. It should be mentioned that recent investigations [Gaunt (41), Talbott (43)] showed that treatment with desoxycorticosterone acetate alone, even when continued over long periods, rarely restores the normal renal function of Addison disease.

IV. LIVER

My last remarks deal with the liver, an organ which like a large reservoir collects considerable quantities of fluid, empties some of it into the great thoracic lymph duct and some into the biliary tract. Liver parenchyma is capable of rapid adaptation to any osmotic requirement and by removing fluid from the plasma causes increased concentration of the blood. This liver function was well demonstrated by Lamson and Roca (44) in experiments on dogs with the Eck fistula. They showed, for instance, that while 25 cc. of physiologic saline are completely eliminated from the blood in a half hour after intravenous injection, dogs with the Eck fistula restore the original blood concentration only after 2 hours, because very little circulating fluid can bypass through the liver. This very important "hydrodynamic" function can be well demonstrated in its effect on the diuretic action of water intake. From the experiments of Priestley (45) it is evident that after rapid (several minutes) ingestion of 2 to 3 liters of pure water, the absorption is completed in 24 to 55 minutes. The primary dilution of blood is, however, very slight, there being, perhaps, an increase of 2 per cent water and a drop of 5 per cent chlorides in the blood. This indicates that the greatest part of this fluid is promptly transferred to the tissues, especially to the muscles, the skin and the liver, to maintain uniform osmotic pressures in the fluids throughout the body. Only after restoration of the oncotic pressure does the diuresis slowly begin and the consumed water is excreted within 2 to 4 hours. Similar results were obtained by Smirk and associates (46) by means of a procedure which enabled them to weigh separately the abdomen and limbs of a human subject, or of an intact animal, after water drinking. After the administration of 1 liter of water the weight of the abdomen was found to increase, then gradually declined for a period of about one half hour to one hour, while the leg weight increased by 1.5 per cent, and diuresis was initiated after all the absorbed water had entered the tissues. It is significant that posterior pituitary extract in these experiments on normal individuals delayed water excretion; the ingested water distributed in the legs was retained in the muscles quite contrary to the hypothesis that the reabsorption of water was accelerated in the tubuli by pituitary extract.

The importance of the liver in this "hydrodynamic" and "osmoregulating" function is demonstrated by dogs with regular Eck fistula [Molitor and Pick (47)], in which blood of the *vena portae* passes directly into the vena cava inferior without liver perfusion. The hydremic portal blood is no longer collected and concentrated in the liver and in the other tissues and we see a quicker and more precipitous course of diuresis than that in a normal dog. On the contrary, when the inferior vena cava is anastomosed with the portal vein, so that besides the portal blood the whole blood of the lower half of the body from the legs and abdominal vessels passes through the liver (reverse Eck fistula), the altered liver induces a very reduced and delayed water diuresis [Kunz and Molitor (48)]. This indicates that the liver, besides its "hydrodynamic" action, has another function in regulating the displacement of water.

It has been known for a long time that serious diseases of the human liver pro-

duce even severe edema and a diminution of kidney secretion, a so-called "opsiuria" (49). Pick and Wagner (50) observed that in the case of a liver tumor with azoamylia, the excretion of water, urea and chlorides was completely disturbed. Chemical and pharmacological attempts [Glaubach and Molitor (51)] to isolate a "liver hormone" and study its effect in the alcoholic liver extracts on water metabolism were successful. An injection of this liver extract produces in a dog with damaged kidney and restricted water secretion an average of 30 per cent increased diuresis and excretion of sodium chlorides and nitrogen. The effective diuretic principle is thermostable, soluble in water and in dilute alcohol and precipitable with neutral salts as well as concentrated alcohol and ether. It may be assumed that further chemical and clinical research will elucidate more the nature of this liver hormone which is obviously important for maintenance of water and salt balance.

A similar kind of liver hormone was successfully used not only experimentally on cats but also clinically in cases of parenchymatosis liver disease, jaundice, arsphenamine hepatitis and in cases of hepatic cirrhosis with ascites, as well as in patients with cardiac congestion [Adlersberg, Zak and others (52)]. After intramuscular administration of a liver extract (Lilly) diluted in saline (5 ml., two times weekly with high protein diet), an increased diuresis, arrest of ascites fluid, or inhibition of its reaccumulation, so that further paracenthesis was unnecessary, was noted by Hoagland and associates (53). Similar experiences were also reported by Oettel (54), who used the preparations "Pernaemyl" and "Hepatopson"; he called this liver hormone "Hepato-Diuretin." According to other clinical reports, cases of renal insufficiency, for instance, certain nephroses showed markedly increased diuresis after liver extract therapy [Porges (55) and Grossman (56)]. Other cases of severe impairment of the water balance resulting in edema, ascites and non-protein nitrogen retention were treated with liver extracts by Hammerschlag (57) with good results.

Another important activity of the liver in relation to water metabolism, demonstrable with diuretic mercury preparations (Salyrgan, Novasurol or Mercupurine), is manifested only in the presence of a normal liver with a good bile secretion. In any disturbance of the bile secretion as in cases of hypocholia, acholia or jaundice or in experimental bile fistulas [Claussen (58)] the mercury diuretics remain ineffective. It, therefore, indicates that these diuretics are complex and need some substances which are built up in the normal liver, perhaps in connection with the bile or the intestinal mucous membrane.

Glaubach and Molitor (51), as Lampe (59), found in one of the alcoholic liver fractions, beside the diuretic principle, an antidiuretic which inhibits the diuresis of the liver hormone. A similar antidiuretic substance was found by White and Theobald (60), Teel and Reid (61), Walker (62) and others (63) in the ox liver. These antidiuretics may be different from the pituitrin antidiuretic because of its resistance to destruction while pitressin is not stable. Products with the same behavior as liver antidiuretics (relative stability with respect to boiling and to treatment with nitrous acid) were found in human urine in cases of eclampsia and in cases of hepatic cirrhosis marked with ascites. It was argued by Ham

and Landis (63) that these antidiuretics were not pituitrin because they do not cause an increased excretion of chlorides, while other authors [Boylstone and Ivy (64), Ingram and associates (12), and Hare and associates (12)] believe the antidiuretic could not be extracted from the urine of animals unless the posterior pituitary or the hypothalamic-hypophyseal system was intact.

As I complete my remarks on the action of principles in the endocrine glands on water and salt metabolism, I hope I have left with you the impression that despite some progress made in the last years in the physiology and pharmacology of the diuresis, many problems still remain unsolved and are awaiting further experimental and clinical work.

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SUPRASELLAR CHORDOMA

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Intracranial chordomas are not rare. Their origin from embryonal residues of the notochord is well understood and their histologic features have been frequently and comprehensively described. However, few chordomas situated in the suprasellar region are recorded and offer difficult diagnostic problems. Even the gross appearance of such tumors in this aforesaid location is not always indicative of their histologic character. On the other hand, familiarity with their structural features is the only reliable aid in their identification, particularly, when biopsied material is studied in the course of surgical intervention.

The following case is described in order to reemphasize some of the already known facts concerning such tumors, and to present them to readers who are not likely to encounter a description of such a case in the general medical literature.

CASE REPORT

History. (Adm. #500192; P.M. #12415) The patient, a man aged 58 years, except for a productive cough of ten years' duration had apparently been well until one and a half years before his admission to the hospital. At that time he developed a burning sensation on the right side of his forehead. A physician observed then that the patient's right eye did not move well and that the right pupil did not react, although vision remained unimpaired. In the course of the next six months the ability to move the right eye gradually diminished and at the end of that time it did not move at all. The patient then complained of seeing double and it was noticed that the right eyelid drooped gradually until the eye closed completely. Six months later the patient began to experience generalized weakness and at the end of another three months, while sitting, he suddenly lost consciousness and fell from his chair. He regained full consciousness ten minutes later. For the following three weeks he was confined to bed and then gradually resumed his normal activities. His recovery was interrupted by another attack of unconsciousness lasting two minutes. This time he was confined to bed for six weeks. During this period he experienced intermittent pain in the inner canthus of the left eye; it was noticed that his left upper eyelid had begun to droop and on several occasions the eye closed completely for periods of a day or two. Three weeks before admission to the hospital the patient, while out of bed, complained of generalized weakness and dragged his right foot. One week later he again passed through an episode of unconsciousness, this time lasting ten hours. On regaining consciousness he displayed increased weakness and complained of pain in the right forearm; his speech was thick. The day before entering the hospital the patient was found in a state of semi-stupor, from which he awakened after four hours. He entered the hospital on January 9, 1943.

Examination. There was a complete right ophthalmoplegia with exophthalmos and inability to open that eye. The left eye moved poorly in all directions, although somewhat better on lateral gaze. Both pupils were large and irregular, the right being larger than the left. The left pupil reacted very slightly to light, the right not at all to light or in accommodation. Vision seemed to be good in each eye. The fundi showed moderate narrowing of the arteries and slight distention of the veins. The right corneal reflex was absent. Sensation of pain was absent in the distribution of the third division, and diminished in the distribution of the first and second divisions of the right trigeminal nerve.

There was a slight right hemiparesis with weakness especially marked in the right arm which, on extension, showed a downward drift. The tendon reflexes were moderately active, slightly more so in the right arm than in the left; the ankle jerks were sluggish. There were Babinski and Chaddock signs on the right, a diminished right cremasteric reflex and absent right abdominal reflexes. Sense of pain was slightly diminished over the entire right side of the body, and there was slight finger-to-nose ataxia on the left.

The general physical examination revealed moderate pulmonary emphysema with scoliosis of the spine and prominence of the thoracic cage on the right posteriorly. At the right apex there was bronchial breathing with scattered moist rales and dullness to percussion. There were also scattered moist rales throughout both lung fields, more marked at the bases. The fingers and toes were moderately clubbed.

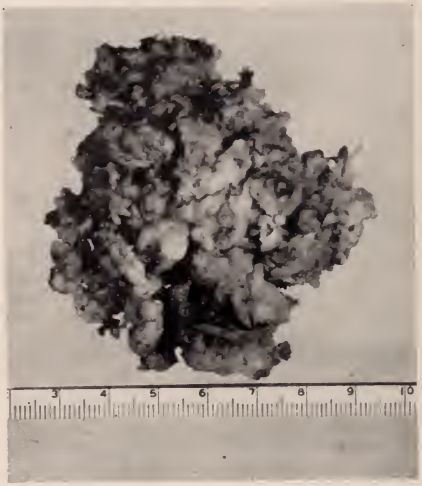

FIG. 1. Gross appearance of the suprasellar chordoma

Laboratory data. Blood: hemoglobin, 75 per cent; white blood cells, 15,200 with 55 per cent polymorphonuclear leucocytes; 39 per cent lymphocytes; 4 per cent monocytes; 1 per cent eosinophiles. Wassermann reaction, negative. Urine: faint trace of albumin, few epithelial cells, occasional white blood cells.

X-ray examination of the skull was found to show "a large mass which had destroyed the sella turcica and extended into the sphenoid sinus. It had eroded the roof and anterior wall of the sphenoid sinus extending into the nasopharynx." The findings were suggestive of a Schmincke tumor.

Electroencephalographic studies gave the impression of a midline lesion involving the hypothalamic structures.

Course. It was felt that the neurologic findings could not readily be explained on the basis of a single lesion. An interpeduncular tumor involving the third, fourth, fifth, and sixth nerves on the right, and the third and fourth nerves on the left, and pressing on the left cerebral peduncle was postulated. However in view of the findings in the chest, a

metastatic carcinoma from a primary lesion in the lungs was regarded as the most likely diagnosis. Pulmonary tuberculosis was suspected and an intracranial tuberculoma was also considered as a possible explanation for the neurological manifestations. Because the x-ray findings suggested a Schmincke tumor, a biopsy of the nasopharynx was performed. This revealed chronic inflammation with no evidence of tumor. Caloric studies pointed to a lesion affecting the central vestibular mechanism.

At the end of his third week in the hospital, on January 23, the patient's temperature suddenly rose to 102°F.; he appeared gravely ill and was placed on sulfathiazole. Five days later the fever subsided, he became more alert, and the drug was discontinued. A course of deep x-ray therapy was instituted. On February 9, the patient exhibited difficulty in swallowing and thereafter became progressively more drowsy. Three days later he could move his left arm only when stimulated. There was considerable weakness of the right arm and some weakness of the right leg, with positive Babinski and Chaddock signs on the right.

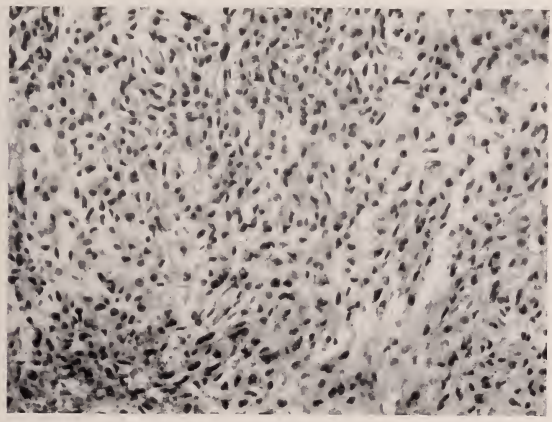

FIG. 2. Section of tumor showing the epithelial character of the cells in its denser areas Photomicrograph; hematoxylin and eosin stain.

All the tendon reflexes became depressed. The right eye did not move. The left eye moved very little; at rest it deviated laterally, but could be brought to the midline; no other motions were possible. There was right sensory and motor fifth nerve involvement. There was a right peripheral facial weakness. The tongue deviated to the left. The patient's condition declined rapidly, and he died on his 26th day in the hospital.

Necropsy findings. Gross. The skull was very thin and fragile. The dura was adherent to the skull, so that the calvarium and brain were lifted off as one piece. The removal of the brain was further impeded by the presence of a large egg-sized, smooth, shiny, multicolored tumor mass (fig. 1) at the base of the brain in the region of the sella turcica. This mass extended to both sides of the midline, but more to the right. Flattened optic nerves were stretched over it. The oculomotor nerves were also markedly thinned, especially that on the right. The sides of the mass were covered by the dura mater except for a small area, where the mass extended upward into the brain. Light brown gelatinous fluid exuded when the mass was punctured. The mass was extremely friable and could be removed from the

floor of the skull only in fragments; it appeared to consist of numerous cysts. After removal of the mass there remained a large defect in the base of the skull.

On sectioning of the brain, the significant findings included marked but asymmetrical internal hydrocephalus, with the right lateral ventricle smaller than the left, probably because of some developmental defect. On tracing the anterior horn of this ventricle it was found to be interrupted in its most anterior part by a membrane so that a small cavity was formed at the anterior portion of the ventricle, entirely separate from the rest of the ventricle. Its lining retained a more primitive appearance. The third ventricle was somewhat elevated in its ventral portion and was markedly dilated.

Microscopic observations. The histologic findings of significance are limited to those encountered in the tumor. Sections obtained from the periphery of the tumor display a somewhat confluent, basophilic cellular mass with deeply stained nuclei distributed in a

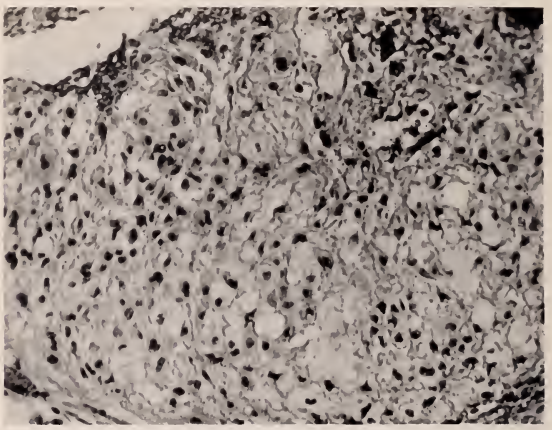

FIG. 3. Tumor cells under higher magnification. Some of the cells have assumed a bladder-like (phasaliforous) appearance.
Photomicrograph; hematoxylin and eosin stain.

fashion suggesting a lobular structure (fig. 2). The cytoplasmic material is abundant, and in some instances provides the cell with a well-outlined circumference and a strong resemblance to an epithelial form. Many of the cells exhibit one or more vacuoles (fig. 3). Under higher magnification and in sections nearer the center of the tumor, the cells are somewhat separated and display a more definite outline. In general the cell form strongly suggests a notochordal derivation (fig. 4). The cytoplasm is abundant, clear, bladder-like (physaliphorous) in shape, with the nucleus eccentric in location (fig. 5). Vacuolization in some of the cells is more pronounced and in some only a few cytoplasmic threads or bands enveloping the vacuoles remain of the cytoplasm. Within some areas of the tumor mass, the primitive character of the tissue and of the cellular activity is shown by the syncytial character of the protoplasmic mass (fig. 6) in which are scattered nuclei with rich chromatin deposits and a tendency to multinuclear formation. Still more striking is the confluency of vacuolized cells into large almost acellular areas filled with a homogeneous, slightly granular substance identified by a specific stain as mucus (figs. 7 and 8). The extent of such areas varies and in some parts assumes unusually large proportions (fig. 8). In other parts of

FIG. 4. A group of unvacuolated tumor cells displaying features most typical of chordoma.
Photomicrograph; hematoxylin and eosin stain.

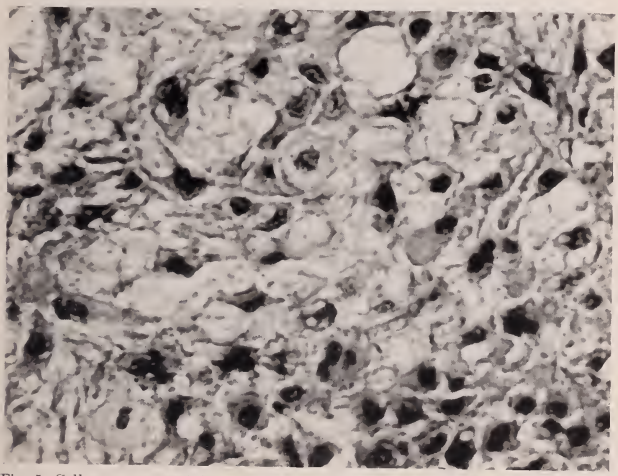

Fig. 5. Cell groups, containing many cells in various stages of characteristic alteration and vacuolization.
Photomicrograph; hematoxylin and eosin stain.

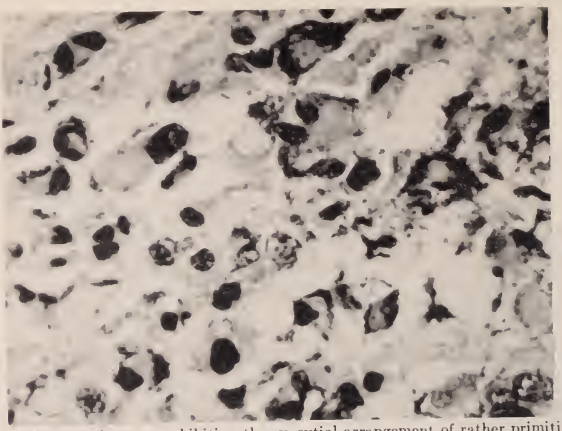

FIG. 6. Section of tumor, exhibiting the synsytial arrangement of rather primitive cell forms.
Photomicrograph; hematoxylin and eosin stain.

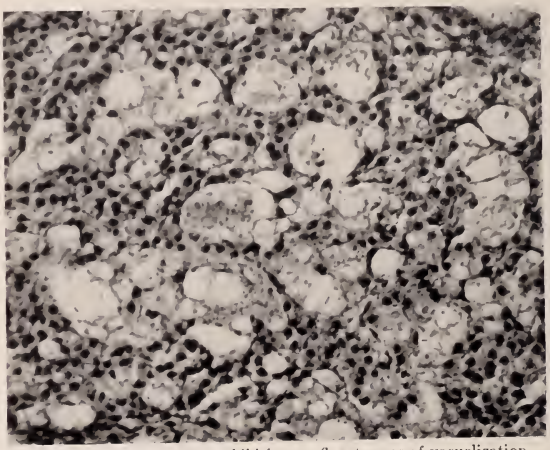

FIG. 7. Section of tumor, exhibiting confluent areas of vacuolization
Photomicrograph; hematoxylin and eosin stain

the tumor the tissue assumes the character of mesenchyme and consists of elongated cells, which interlace with one another forming a loose meshwork (fig. 9). In proximity to such tissue there are seen areas in which nuclei are deposited in a hyaline matrix as though lodged

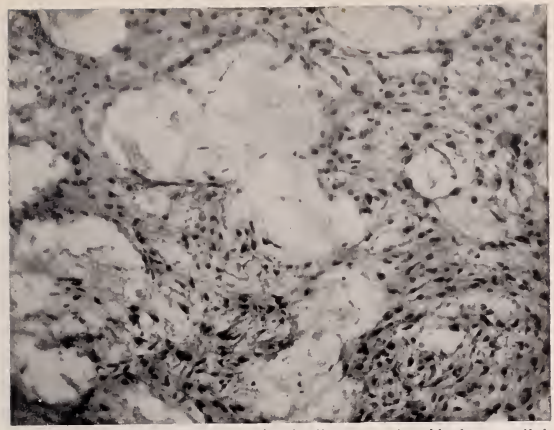

FIG. 8. Section of tumor, in which vacuolized cells were replaced by large acellular areas filled with a homogeneous, slightly granular (mucinous) substance.
Photomicrograph; hematoxylin and eosin stain.

FIG. 9. Section of tumor, showing mesenchymatous tissue consisting of interlacing fibroblast-like cells.
Photomicrograph; hematoxylin and eosin stain.

in lacunae (fig. 10). In still other areas the tissue assumes the character of hyaline cartilage (fig. 11). In these regions particles of well formed bone are often encountered.

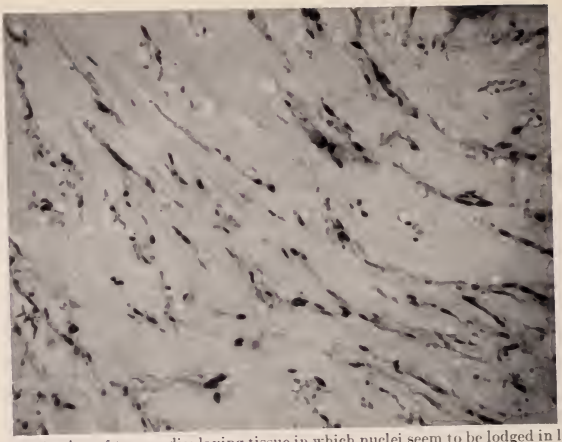

FIG. 10. Section of tumor, displaying tissue in which nuclei seem to be lodged in lacunae and are deposited in a hyaline matrix.
Photomicrograph; hematoxylin and eosin stain.

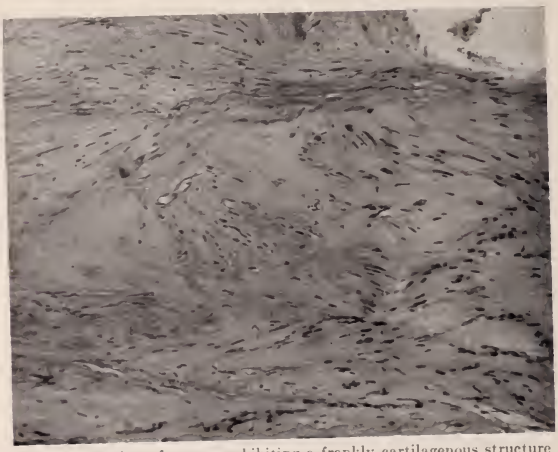

FIG. 11. Section of tumor, exhibiting a frankly cartilagenous structure
Photomicrograph; hematoxylin and eosin stain

GENERAL COMMENT

Virchow was first to observe the not infrequent occurrence of a jelly-like excrescence at the clivus, the spheno-occipital synchondrosis. He regarded it as a

product of degeneration of cartilage and named it *echondrosis physaliphora spheno-occipitalis*. Shortly afterwards, Mueller traced it to embryonal residues of the notochord. It was Ribbert, however, who years later produced experimental proof for the ultimate origin of this type of tumor and who named it *chordoma*. Horwitz, reviewing the embryology of the notochord, emphasized the relationship of several phases of the development of this structure to tumor formation, and to the observation that in the course of its involution notochordal offshoots become separated from the main stem and are driven to the periphery by a tension similar to that which compresses the intravertebral portion of the notochord. This heterotopic vestige of notochordal masses, thus displaced in the various regions of the spinal column as well as in the several cranial bones, serves as the source for the formation of *chordomas*.

It is obvious, therefore, that chordomas may be formed all along the vertebral column, though they are most frequently encountered at the ends of the axial skeleton: the sacro-coccygeal region or the basilar plate at the clivus.

All those who have investigated this type of tumor and reviewed the literature agree that a little over one-third of recorded chordomas have been discovered in the cranial cavity: of 250 reported cases, 90 were intracranial in origin and location. Of those intracranial in origin some may grow down by way of the cranio-pharyngeal tract into the pharynx, others decompress themselves through the foramen magnum into the intraspinal canal, while still others expand forward in the suprasellar space and ultimately find their way into the orbit.

In gross appearance, the tumor is usually a reddish brown or pale gray, lobulated and pedunculated mass. It is often soft and semi-transparent, but occasionally firm. It frequently envelopes, compresses and displaces structures at the base of the brain (vessels, cranial nerves, pons, medulla, etc.).

Benign and malignant forms of chordoma are described. The critical location and inaccessibility of the tumor should perhaps place all of the chordomas in the malignant group. Histologically, however, there is some justification for such a division. In general the chordomas recapitulate the several phases in the development and involution of the notochord.

There are cells duplicating those found in the early phase of notochordal differentiation; they are solid, polygonal, epithelial cells exhibiting a well-defined cell membrane, abundant cytoplasm and a well-stained central nucleus. Many of the cells assume a bladder-like outline, hence the term "physaliphorous" is often used to describe them. Areas of solid epithelial cell-sheaths alternate with areas in which the cells begin to display vacuolization (an early stage in notochordal involution). These, in turn, alternate with areas in which cells have assumed a syncytial character (the cell outlines are no longer visible). Finally, large, rarefied areas are encountered in which no cell structure is recognizable, the space being occupied by mucinous material, which is said to be rich in glycogen.

A Few Clinical Data. It is difficult to recognize clinically an intracranial chordoma, but this type of lesion should be borne in mind whenever a gradual onset of nasopharyngeal and intracranial symptoms makes its appearance in a middle aged patient. More specifically, an intracranial chordoma should be

suspected in the presence of a syndrome comprising the following: a midline obstructive nasopharyngeal tumor; bilateral palsies of several cranial nerves; and motor and sensory manifestations of compression of the brain stem with but little or no evidence of increased intracranial pressure.

X-ray evidence of a destructive non-productive bone defect in the clivus extending from the sella turcica to the foramen magnum, assuming a characteristic V-shaped notch in the basilar plate favors such a diagnosis.

As to therapy, little may be said, except to refer to Von Wagenen (15), who offers a surgical approach for the removal (partial, of course) of such tumor in the hope of prolonging life.

In differential diagnosis, several other types of expanding lesion in an approximately similar location need be considered. They include: suprasellar meningioma; craniopharyngeoma; and pituitary adenoma.

Suprasellar meningiomas are usually associated with an intact base of skull, primary optic atrophy, and menstrual disturbances (they are most commonly encountered in middle aged women).

In craniopharyngeomas, significant findings are calcification in the para or suprasellar region and manifestations of hypothalamic disturbances as dwarfism and diabetis insipidus, etc.

Pituitary adenomas are readily differentiated by signs of anterior pituitary dysfunction (acromegaly), by visual field disturbances, optic atrophy and enlargement of the sella turcica.

SUMMARY

A case of intracranial chordoma is described. Its origin from the embryonal residues of the notochord is reviewed. Its histologic features are described and illustrated; they recapitulate the several phases in the development and involution of the notochord in man. Reference is made to the clinical manifestations of this type of intracranial neoplasm.

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HYPERTENSION DUE TO PERIRENAL CONSTRICTION

Case Report[1]

NAOMI de SOLA POOL, M.D.[2]

Following the demonstration by Goldblatt and co-workers (1) of the experimental production of hypertension in the dog and rat by renal ischemia, there appeared a number of case reports of human hypertension with unilateral kidney disease in which the Goldblatt mechanism was invoked to account for the elevation of blood pressure. Blatt and Page (2), Freeman and Hartley (3), Saphir and Ballinger (4), Farrell and Young (5), and others have reported such cases. In the ensuing years most of these cases have been reclassified and re-evaluated and the hypertension has rarely been accepted as being due to the Goldblatt mechanism. Goldring and Chassis (6), after a careful scrutiny of reported cases, came to the conclusion that the Goldblatt mechanism is very rarely the cause of human hypertension. The cases just cited are among those which have withstood critique; Freeman's case being an example of vascular obstruction comparable to the Goldblatt clamp, Saphir's first case being an example of arterial obstruction plus external compression, and the cases reported by Blatt and Page, and Farrell and Young are examples of renal compression comparable to the cellophane envelope method of Page and Graef (7).

The mechanism of renal ischemia as the cause of hypertension is now fully established and is well illustrated by the following case.

History. The patient, a boy aged eleven, was observed and treated successfully at the Pediatric Clinic one year earlier for obesity by diet only. At that time physical examination was negative.

At the end of that period, his father noted that the patient's left tonsil was enlarging rapidly. Because of the huge size of the left tonsil, a tonsillectomy was performed. The physical examination at this time revealed only a few pea sized nodes at the angle of the jaw. The blood pressure was 100 systolic and 64 diastolic. The pathological report was lymphosarcoma of the tonsil. Careful search revealed no other focus of lymphosarcoma. The patient was referred to the radiotherapy department for further treatment.

He remained in apparent good health for the subsequent three months and then following an episode of vigorous laughing, he developed a sharp pain in the right groin with swelling and tenderness. Four days after the initial episode he was admitted to the hospital in severe acidosis; the day before admission he began to vomit persistently.

Examination. The patient, an obese boy of eleven, appeared acutely ill and dyspneic. He was drowsy and uncooperative. There was no generalized lymphadenopathy. His blood pressure was 150 systolic and 100 diastolic. Repeated blood pressure readings showed persistent elevation with the systolic ranging from 140 to 160 and the diastolic ranging from 95 to 105. A mass was felt two fingers below the costal margin on the left. In the right groin was a tender, elongated mass, and on rectal examination a large, hard, nodular mass was felt protruding into the lumen. The urine gave a four plus reaction for acetone; it

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[1] From the Laboratories of the Mount Sinai Hospital, New York, Division of Pathology. Presented at the meeting of the New York Pathological Society, November 29, 1945.

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FIG. 1. Left kidney with surrounding tumor

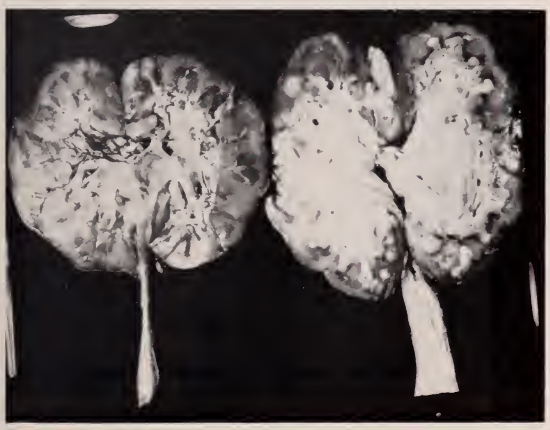

FIG. 2. Cross section of both kidneys, the left showing tumor infiltration

contained no albumin or sugar. The blood urea nitrogen was 23 mg. per cent and the CO_2 was 22 volumes per cent.

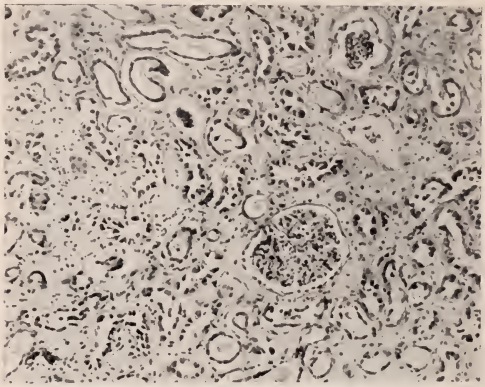

FIG. 3. Cortex of left kidney, showing increase of interstitial tissue, dilatation and atrophy of the convoluted tubules, and normal glomerulus.

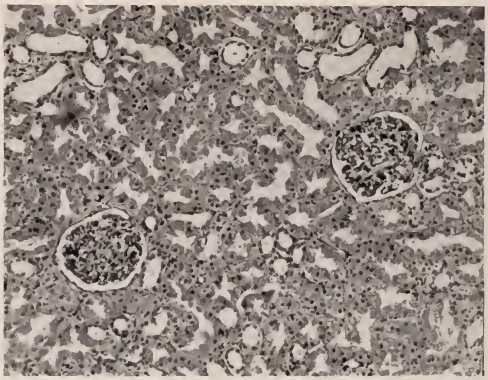

FIG. 4. Cortex of right kidney showing no change

Course. Treatment to combat the acidosis was begun at once. The patient was failin rapidly. There was a daily increase in the palpable masses in the abdomen. On the eight day in the hospital the child bled from the nose and mouth and expired shortly thereafte

Postmortem findings. The abdominal cavity contained about 1500 cc. of cloudy yellow

ish fluid. The parietal peritoneum and deep fascia were infiltrated with greyish white, homogeneous tumor tissue. The entire mesenteric and omental fat was likewise infiltrated. There was a mass of nodes at the root of the mesentery which was soft and hemorrhagic. There was extensive infiltration of the retroperitoneal tissues by tumor. The lungs contained a fair amount of aspirated blood. The right kidney and adrenal appeared normal. The left adrenal could not be recognized due to tumor infiltration. The left kidney was completely enveloped by tumor (fig. 1). The hilus was infiltrated by tumor and the medulla was almost completely replaced by it (fig. 2). The left renal vessels were similarly infiltrated and tumor tissue bulged into the lumen of the renal vein. The ureters and bladder also showed tumor infiltration. No tumor tissue was found in the nasopharynx.

Microscopic observations. There was extensive infiltration of all retroperitoneal tissue with lymphosarcoma. There was no evidence of nephritis. The right kidney was normal in every respect (fig. 3). The left kidney, in areas not replaced by tumor, showed only a striking increase in the interstitial tissue similar to that observed in the experimental Goldblatt preparations (fig. 4).

DISCUSSION

The incidence of hypertension in renal tumor cases has been estimated by Braasch (8) to be between 27 to 29 per cent, but on further analysis of his series by age groups, this is approximately what one would expect in any similar control group (9). The case reports by Blatt and Page, and by Bradley and Pincoffs (10) are among the few reports of hypertension due to renal involvement by tumor. Cases of hypertension in childhood associated with unilateral kidney diseases have been reported in such instances as ectopic kidney (11), and congenital vascular anomalies (12). These instances in which the Goldblatt mechanism may be used to explain the elevated tension are extremely rare.

CONCLUSIONS

In the case presented here, it has definitely been established: 1) that the blood pressure prior to illness was normal. 2) That on readmission with diffuse, generalized lymphosarcomatosis the blood pressure was persistently elevated. 3) That the only lesion found at autopsy to account for this change, was encasement of the left kidney in a mass of tumor tissue with encroachment on the vascular supply.

There was no evidence of renal disease other than tumor infiltration, and one may therefore assume that this is a case of hypertension in a child caused by renal compression and ischemia.

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PERICARDIECTOMY FOR CONSTRICTIVE PERICARDITIS*

Case Report

WILLIAM HITZIG, M.D.

When medicine fails in the treatment of heart disease, as it sometimes does, the cardiologist has to turn to his surgical colleague for assistance. As hazardous as heart surgery is, yet notable triumphs have been made within recent years in pericardiectomy for constrictive pericarditis. Although this is probably one of the most dramatic procedures in surgery of the heart, the accurate diagnosis of constrictive pericarditis is no less thrilling than a successful operation.

The following case which came under observation in June, 1940, represents a follow-up study of over five years. Its successful outcome is a tribute to modern cardiac surgery.

History: (Adm. #458359). N. B., a 23 year old clerk, entered the hospital in June, 1940. Two and a half years previously a physical examination revealed no abnormalities. Five months before admission increase in the size of the abdomen was noted. Two months later a physician diagnosed fluid in the abdomen and a hydrocele developed. Because of this a malignant tumor of the testes was suspected while under observation in a Pennsylvania hospital. He was referred to my office for examination and a diagnosis of constrictive pericarditis was made on the basis of venous hypertension, ascites and a small heart. He was referred to the hospital for pericardiectomy.

Examination: The patient did not appear ill. There was no dyspnea nor orthopnea. The cervical veins were distended, filling from below in the sitting position. A marked hepatojugular reflex was present. The lower chest bulged, due to abdominal distension by a large amount of fluid. The heart sounds were of good quality, the second aortic sound was louder than the second pulmonic sound. The blood pressure was 126 systolic and 96 diastolic. A non-tender liver was palpated three inches below the costal margin. A small left-sided hydrocele was present. There was no edema.

Laboratory data: The venous pressure was elevated as had already been noted before admission. Studies which cannot be detailed here proved that, according to circulatory dynamics, the existence of right heart failure was definitely established. The electrocardiogram revealed bradycardia and a tendency to right axis deviation, low T waves and notched P waves. Electrocardiograms taken in the left lateral position caused a more marked right axis deviation; in the right lateral position the right axis deviation disappeared. The roentgenogram of the chest revealed no abnormality in the lungs or pleura. The diaphragm appeared slightly elevated, the cardiac silhouette was of small size. On fluoroscopic examination there was no evidence of enlargement of the left auricle. The x-ray showed a distinct diminution in the pulsations of the left heart border. Fairly good pulsations were noted over the remainder of the cardiac shadow. On contrast visualization of the cardiac chambers with diodrast, both ventricles showed considerable dilatation.

Course: Shortly after admission the patient's weight was 143 pounds. Treatment with mercupurin, digitalis, and ammonium chloride, and restriction of fluids caused a progressive drop in weight to 126 pounds. Because the diagnosis appeared established and there was no other known curative therapy, operation was decided upon.

Operation: (July 19, 1940) The heart was approached from the left side through a liberal transthoracic incision. An immobile whitish pericardium of no great thickness was

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encountered. Extensive piecemeal removal of freed flaps of thickened pericardium was carried out. The heart bulged and pulsated vigorously. A thin, grayish-white layer which was wrinkled on contraction was still visible over the left heart. After freeing the left heart, the pericardium was dissected away from the right heart. The large vessels at the base of the heart were not visualized.

Post-operative Course: There was an abnormal venous pressure curve for many months although ascites disappeared and never recurred. The patient gradually improved in health, his exercise tolerance improved, and his venous pressure gradually assumed a lower range. He obtained a job in the hospital and was able to pursue a gainful occupation without physical distress. During the recent war he even expressed a strong desire to join the armed forces of his country, but because of the history of the previous heart operation he was rejected.

COMMENT

This case illustrates the well-known fallibility of the electrocardiographic method of determining the mediastinal fixation of the heart, an aid in the diagnosis of constrictive pericarditis. Evidently fixation of the heart is not necessarily an accompaniment of constrictive pericarditis; it occurs only when there is an added factor, namely, the factor of external pericarditis which anchors the immobile heart to adjacent structures.

LEFT SUBPHRENIC ABSCESS*

Case Report

ERNEST E. ARNHEIM, M D.

The pathological and clinical features of left subphrenic abscess, based on a study of 33 cases observed at The Mount Sinai Hospital from 1928 to 1942, have been reported by Neuhof and Schlossmann (1). The following case is the only one in that series in which the etiology had not been determined. Recovery followed a one stage transpleural, transdiaphragmatic drainage, and the patient has remained well for four and one-half years.

History. (Adm. # 474718) D. F., a man, aged 68 years, was admitted to the hospital on June 11, 1941. The patient was well until four months before admission when he had diarrhea for one week. Thereafter, he noted anorexia, weakness, and a gradual loss of about 20 pounds in weight. On two occasions in the three months prior to admission there were brief episodes of periumbilical pain. Four nights before admission, he was awakened by a chill. On each of the following four days there was a chill, followed by a rise in temperature to 103°F. Cough and slight pain in the left shoulder were noted for two days.

Examination. The temperature was 99.8°F., and the pulse rate, 88. Evidences of arteriosclerosis and loss of weight were present. No other abnormalities were noted except on abdominal examination which revealed spascity without tenderness on the right side. Slight percussion tenderness was elicited over the liver, and the spleen was palpable one inch below the costal margin. Enlargement of the prostate gland was found on rectal examination.

Laboratory data. Urinalysis revealed no abnormalities except for a trace of albumin. Blood examination showed hemoglobin, 80 per cent; white cells 10,600, with segmented polymorphonuclear leukocytes 37 per cent, nonsegmented polymorphonuclear leukocytes 38 per cent, lymphocytes 20 per cent, eosinophiles 3 per cent, and monocytes 2 per cent. The icterus index was 6; urea nitrogen, 19 mg. per cent; sugar, 100 mg. per cent; protein, 5.8 mg. per cent. The sedimentation rate was 35 minutes. The gastric test meal revealed free hydrochloric acid 20 and total acids 36. The following tests gave negative results: Wasserman, Mantoux (1:100,000), stool for guaiac, and agglutination for typhoid and dysentery.

Intravenous pyelography revealed no abnormalities. X-ray examination of the pelvis showed irregular, sclerotic changes and small areas of rarefaction in the left ossinnominatum, suggestive of Paget's disease, with the possibility of metastatic malignancy to be considered. The colon was normal by barium enema examination.

Course. The highest temperature during the first six hospital days was 100.6° F. On the seventh day there were two chills, with a rise in temperature to 105.2°F. A blood culture revealed a growth of gram-positive cocci in one flask, later reported as streptococcus intermedians (anaerobic). During the second week there was daily fever, varying between 101°F. and 104°F. The patient complained of some pain in the left upper quadrant of the abdomen and the left flank and there was slight tenderness in these regions. On the eighth day the motion of the left diaphragm was noted to be restricted on fluoroscopic examination. The white blood cell count rose to 21,450, with segmented polymorphonuclear leukocytes 50 per cent.

On the tenth hospital day x-ray examination of the stomach revealed a defect on the greater curvature in the region of the cardia, interpreted as being due to an extragastric

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mass. An x-ray of the chest (fig. 1), on the same day, showed a marked elevation of the left diaphragm, with a small pleural exudate at the left base; there was a slight widening of the right superior mediastinum.

On the fourteenth hospital day physical signs of fluid in the left pleural cavity were noted. Aspiration of the left side of the chest in the posterior axillary line (with a deep injection needle) yielded foul-smelling pus, the smear of which revealed many gram-positive cocci. The culture of the pus was subsequently reported streptococcus nonhemolyticus. The patient was transferred to the surgical service and an operation was performed four hours after aspiration.

Operation. (June 24, 1941) The chest was aspirated in the left eighth intercostal space in the posterior axillary line (the site of previous aspiration); no fluid was obtained. As-

Fig. 1

piration in the ninth intercostal space, fairly superficially, was productive of brown, purulent fluid.

Under local anesthesia, about 3 inches of the ninth rib were excised posteriorly, the anterior limit of excision being at about the posterior axillary line. The parietal pleura was normal in appearance. The pleural space was opened and found to be free of infection. Pus was noted on the diaphragm at the site of the puncture produced by the aspirating needle which had transversed the diaphragm. The diaphragm was sutured to the musculature bordering the thoracic incision by continuous sutures of chromic catgut. The pleural space could not be closed off at the posterior limit of the incision because of tension on the sutures. In view of this, and the possible contamination of the pleura by previous aspirations, a small, rubber tube was placed in the pleural cavity posteriorly for closed drainage. Iodoform packings were placed around the tube down to the pleura. The diaphragm was incised and a large subphrenic abscess was entered. The abscess contained

about 1 liter of thick, brown, non-foul pus; there was some clotted blood and necrotic, purulent exudate in addition to the pus. The cavity was multilocular, the largest recess passing toward the right side for a distance of about 4 inches. No anatomical structures were identified within the abscess. Pus was aspirated from the numerous locules, and the cavities were widely packed with stips of iodoform gauze. The thoracic wound was packed with iodoform gauze.

The report from the pathological laboratory was: "disorganized fragments of necrotic fibrous tissue, possibly derived from spleen; necrotic purulent exudate."

Post-operative course. The highest temperatures were 103.6°F. on the first post-operative day, 103.2°F. on the second day, 101°F. on the third day, and 100°F. on the fourth to the eighth days. The temperature was normal after the first week. An intravenous in-

Fig. 2

fusion of 5 per cent dextrose in isotonic solution of sodium chloride was given during the first two days. Sulfathiazole was administered from the second to the seventh days.

During the first two post-operative days, 270 cc. of serosanguinous fluid drained from the left pleural cavity through the closed drainage system, after which the closed drainage was discontinued. The tube was removed from the left pleural cavity on the seventh day. At this time the packings were removed from the subphrenic space which appeared clean and granulating. Thereafter, the cavity was packed at intervals, and rapidly became smaller in size. The patient was out of bed on the seventh day.

X-ray examination of the chest on the third post-operative day revealed a small effusion and some air, with two fluid levels, in the left pleural cavity; opaque packing was noted in the left subphrenic space. On the sixteenth day an x-ray of the chest showed a small exudate at the base of left pleural cavity.

On the twentieth post-operative day an x-ray following the injection of iodized oil into

the wound revealed two cavities, each measuring about 3 cm. in width, communicating by a narrow tract. The upper cavity appeared to be just above the diaphragm, and the lower cavity below the diaphragm.

X-ray examination of the stomach on the twenty-ninth post-operative day showed a more normal contour at the site of the defect on the greater curvature previously noted.

The patient was discharged in good condition on the thirty-third postoperative day. The wound was healed except for a superficial granulating area.

Follow-up examinations were performed at intervals during the past four and one-half years. The patient has remained well. X-ray examinations of the chest two years and four and one-half years after operation (figs. 2 and 3) revealed a slight elevation of the left leaf of the diaphragm anteriorly by adhesions; there were no abnormalities of the

FIG. 3

lungs or pleura. The widening of the superior mediastinum is unchanged and is probably due to an enlarged right lobe of the thyroid gland.

COMMENT

The slow evolution of the vague clinical features of four months duration and the sudden transition to the active phase of four days duration is of interest, and has been described in the majority of cases of left subphrenic abscess reported by Neuhof and Schlossmann(1). Combined abdominal and thoracic manifestations were observed. The first direct evidence of a left subphrenic abscess was restriction of motion of the left leaf of the diaphragm on fluoroscopic exam-

ination. The diagnosis was confirmed by the roentgen evidence of elevation of the left diaphragm. The roentgen observation of a defect on the greater curvature of the cardiac end of the stomach is of interest.

A complicating empyema was erroneously diagnosed because of the finding of pus on aspiration of the chest. This illustrates the ease with which the diaphragm may be penetrated by the aspirating needle when the leaf of the diaphragm is elevated. Fortunately, pleural contamination did not occur, but in any case of suspected subphrenic abscess it is safer to perform the aspiration in the operating room, and to leave the needle as a guide for operation.

The operative procedure followed, in the main, the technic of a one stage transpleural transdiaphragmatic drainage described by Neuhof (1). An even more anterior approach would have been more direct and would have allowed complete shutting off of the pleura, thus obviating the necessity for closed drainage of the pleura.

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RIGHT SUBPHRENIC ABSCESS WITH PERFORATION INTO THE LOWER LOBE OF THE LUNG*

Case Report

ARTHUR H. AUFSES, M.D.

Although a thoracic suppurative process practically never perforates through the diaphragm into the peritoneal cavity, it is not unusual for subdiaphragmatic purulent collections to perforate upward and enter the lung and bronchial tree. It is quite characteristic for these perforations to occur without producing an empyema. It is likely that, because of the length of time necessary for the infection to erode through the diaphragmatic musculature, a fibrinous pleuritis occurs between the lower surface of the lung and the superior surface of the diaphragm, thereby sealing off the area from the general pleural cavity.

The existence of a bronchial communication may be discovered in various ways. In some instances, the expectoration of a large amount of purulent material may be the first symptom in the course of a cryptic subdiaphragmatic infection. In the following case, the presence of a bronchial fistula was not suspected until one week after the subphrenic abscess had been drained, and the wound was being irrigated. Pulmonary symptoms throughout the entire course of the disease were so slight that they alone would not have led to the diagnosis.

History: (Adm. #494089). A white locomotive engineer, aged 40 years, was admitted to the surgical service on January 6, 1941, for treatment of a right subphrenic sinus communicating with the bronchial tree. On October 10, 1940, while recovering from a drinking bout of the previous evening he was seized with severe abdominal pain, and fever. Three hours later his physician found generalized abdominal rigidity with some distention. Eight hours after the onset, he was seen by a surgical consultant, who found marked rigidity and tenderness localized to the right upper quadrant. There was also marked pain on respiration, indicative of diaphragmatic irritation.

A definite diagnosis could not be made, and in view of the localization of the process, further observation was decided upon. The symptoms and temperature subsided within forty-eight hours, and the patient returned to work. One week later, he again had fever and pain in the right upper quadrant. Physical examination revealed a large collection of air over the liver, and x-ray examination (fig. 1) showed two large fluid levels at the base of the right chest. Above the upper level, there was a curved shadow, with its convexity upward; it was impossible to differentiate between an infra- or supra-diaphragmatic collection.

An operation was performed at another hospital. Drainage was performed anteriorly because the physical signs showed the air to be present in this area. A large subphrenic abscess was found, extending posteriorly and over the dome of the liver. The pleura was not entered at this procedure.

Following drainage, the patient improved rapidly, the temperature returned to normal and the abscess cavity showed evidence of rapid healing. On the seventh post-operative day, while the wound was being irrigated, the patient was suddenly seized with a severe

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Fig. 1. Elevated right diaphragm with two subdiaphragmatic fluid levels

Fig. 2. Plate reversed. Lipiodol injection through sinus entering bronchial tree

cough, and expectorated some of the irrigating fluid. This was the first manifestation of a bronchial communication.

Nevertheless, the wound continued to heal, and the patient was discharged. His general condition continued to improve and he had no cough or expectoration. The wound gradually closed down to a sinus but this did not heal and he was therefore admitted to Mount Sinai Hospital

Examination: Upon admission, physical examination was negative except for a draining sinus in the lower axillary part of the right chest. Lipiodol instillation (fig. 2) into this sinus revealed it to pursue a short tortuous course for about two inches; the oil then outlined a large, irregular cavity about three inches in length and one and one-half inches in width situated above and mesial to the external opening of the sinus. Above and anterior to this cavity, there was a dense shadow, with an upper convex border. Whether this shadow was above or below the diaphragm could not be definitely stated. The lipiodol had also entered the bronchial tree, outlining all the branches of the right lower lobe. These showed no abnormality.

Operation: Two days after admission, the wound was revised. Further rib excision and removal of soft parts revealed a cavity which extended posteriorly and mesially from the sinus opening. The diaphragm was recognized as forming the roof and lateral wall of the abscess cavity. It was opened widely to provide adequate drainage. Three ounces of foul-smelling pus was evacuated. No bronchial fistula could be demonstrated. A small loculation containing pus was found in the thoracic parietes, extending posteriorly, superficial to the diaphragm, in the region of the costo-phrenic sinus. The entire area was packed.

Post-operative Course: X-ray examination performed after several days with radio opaque packing in the abscess, showed it to be apparently well drained, and the diaphragm appeared at almost normal height. Nevertheless, because of retention in the wound, another revision was performed on January 12, 1941. In this procedure, segments of the next two ribs above were removed as far forward as the costal cartilages. In this manner, the entire abscess cavity was completely unroofed. No further sinuses could be found. Once again, no bronchial communication was evident. The dome of the liver was covered by granulation tissue and there was no evidence of intrahepatic pathology. The postoperative course was uneventful, and the patient was discharged on January 22, 1941. The wound subsequently healed completely.

A follow-up x-ray examination on August 10, 1942, at which time the patient was perfectly well, showed no evidence of any residual pathology.

COMMENT

The etiology of the subphrenic abscess in this case was not entirely clear. Because of the large amount of air in the abscess cavity, it was thought to be due to a perforation of a hollow viscus which sealed itself over and never gave rise to any further symptoms. The bronchial communication was of little clinical significance and might never have been recognized had not the wound been irrigated. It was only at the time of irrigations that cough and expectoration were present. Otherwise there were no pulmonary symptoms.

PERFORATION OF ESOPHAGEAL FOREIGN BODY INTO LUNG; PUTRID PULMONARY ABSCESS*

Case Report

H. HENNELL, M.D.

History. (Adm. #54102) A man, aged 61 years, was admitted to the hospital on October 26, 1945 with cough, foul-smelling expectoration, upper chest pain and low-grade fever of three weeks duration.

Three weeks before admission to the hospital, while eating fish, a fish bone stuck in the patient's throat which he could not dislodge by hawking or swallowing food. Almost immediately he began to have pain in the region of the upper sternum which radiated directly backwards. The pain was constant, severe and knife-like. He consulted his family physician the next day but obtained little relief. On the day following he felt generally ill, and then the pain became excrutiating. His physician was again called and a "heart attack" was suspected. This severe pain lasted until the fifth day. After that it was present only after coughing. On the third day after the accident he began to cough and raise increasing amounts of colorless sputum, up to 1½ ounces in 24 hours. The sputum became foul on the fourth day of his illness. A low-grade fever, 100.5°F. rectally, developed early and persisted to the time of his admission to the hospital.

Examination. The significant findings on admission were as follows: The patient did not appear very ill. His cough was moderately severe and the sputum expectorated was foul-smelling. There was no pain or tenderness in the region of the upper mediastinum or over the posterior aspect of the right upper lobe—the site of the intrathoracic process disclosed solely by the x-ray examination.

X-ray examination. The appearance of the lesion was not characteristic. The shadow in the right upper chest, adjacent to or in the mediastinum appeared larger in successive films. This shadow did not have the appearance usually seen in putrid lung abscess of bronchogenous origin.

Course. In view of the history and the other clinical features of the case, this shadow was interpreted as one cast by a putrid pulmonary abscess resulting from a direct invasion of the lung via the mediastinum by a fish bone which had perforated the esophagus. Because of this interpretation it also appeared reasonable to assume that no pleural adhesions over the lesion could be anticipated, and the operation had to be planned accordingly.

Pre-operative esophagoscopy showed a lesion in the esophogus 22 cm. from the upper teeth. There was a 3 mm. depression on the posterior wall with edema and granulation tissue apparently the result of the injury by the fish bone. Bronchoscopy performed at the same time revealed foul-smelling pus coming from the posterior branches of the right upper lobe.

Operation. The patient was, therefore, subjected to operation for a putrid lung abscess. In his description of the operation Dr. H. Neuhof stated the following: "A paravertebral incision immobilizing the scapula was made and two ribs (fourth and fifth?) close to the spine were excised in order to obtain access to the deeply situated lesion. The latter was a bulge of the lung immediately adjacent to the assumed situation of the esophagus and just lateral to the aortic groove. The customary elastic feel of an abscess was not noted. The bulge was aspirated and foul pus under tension was encountered. The tract was split open and a small abscess about one inch in diameter with ill defined limits was laid open. The appearance did not resemble that of a bronchogenous pulmonary abscess. A bronchial blow

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was noted. The abscess cavity was packed. Before the abscess was drained, the entire pleural space was carefully shut off by large pads and packings. This appeared to assure against contamination of the free pleural cavity."

The post-operative course has been uneventful. The patient is ambulatory and free from all pulmonary complaints. Healing is progressing favorably and a cure is confidently anticipated.

COMMENT

The following features of the case may be emphasized:

1. The severe knife-like pain in the upper sternal region radiating directly backward is characteristic of perforation of the esophagus by a foreign body.

2. The abscess of significant mediastinitis which indicated that immediate and direct perforation of the lung from the esophagus took place with prompt formation of a putrid lung abscess.

3. The absence of parietal pleural pain and tenderness over the lung abscess area and the non-characteristic appearance of the lesion suggested a mediastinal and not a bronchogenous origin.

4. The manner in which this truly deep-seated lung abscess was approached successfully in a one-stage operation.

ESSAYS ON THE BIOLOGY OF DISEASE[1]

ELI MOSCHCOWITZ, M.D.

Chapter 16

MYELOMA

Although myeloma is no longer as rare as it was formerly deemed, the biology of the disease is nevertheless only dimly understood, because the opportunities to witness the evolution from its very beginnings come but rarely. Moreover like all malignant neoplastic diseases, the malady is dormant long before sufficiently diagnosticable manifestations appear. Myeloma possesses a comparatively long life cycle and although the average duration of life from the onset of clinical manifestations is between two and three years, reports of durations of five to ten years are by no means rare; in one case it was 14½ years (1).

The following presentation is based on a few personal observations and a study of reported cases. We do not propose to review all the manifold clinical signs and symptoms of this fascinating disease, but only those that may have a biological significance.

1. *Pathologic Anatomy.* In most instances, the first symptom is pain, localized to one or other area of the skeletal structure, and usually x-ray examination reveals multiple areas of rarefaction throughout the bony structures. However diffuse myelomatosis may occur without positive x-ray evidence, as shown by biopsy and especially by sternal puncture. There have been frequent reports of solitary myeloma (2, 3, 4, 5) which are supposed to have a better prognosis than the generalized form. Such solitary myeloma may easily be confused with hyperparathyroidism. Most of these solitary myeloma were reported before diagnostic sternal puncture was available, and without an adequate follow-up. Since then the number of reports of "solitary" myeloma has dropped appreciably; first, because sternal puncture reveals generalized involvement (3) and second, because a follow-up showed both clinical and x-ray evidences of general involvement. Such a study necessitates many years of observation. Thus King (2) reports a patient who, five years after removal of a solitary myeloma of the hip, showed involvement of multiple ribs and Bence-Jones protein in the urine. The patient felt well and was still alive at the last report. Vihvelin's patient (6) was alive 12 years and felt well following removal of a solitary myeloma, although clinical evidences of a generalized "recurrence" were clear. It is apparent, therefore, that the reports of solitary myelomata, both as regards its validity as an entity and its prognosis must be viewed with skepticism. Obviously we

[1] This is the sixteenth chapter in a series of essays by Dr. Eli Moschcowitz, in which an attempt will be made to interpret certain forms of chronic disease from the biologic viewpoint, as opposed to the current trend toward rigid classifications implying a concept of disease as a more or less static phenomenon.

According to present plans, these essays will appear in consecutive issues of the Journal of The Mount Sinai Hospital. When the publication of the projected series of essays is completed, the several installments will be assembled and printed as a monograph.—Ed.

have no way of determining whether myeloma begins as a localized disease or multicentrically. In its terminal phases it is always diffuse.

Although the disease is usually limited to the bone marrow, extraosseous growth, especially of the lymphatic structures, have been reported and when these represent the original manifestations of the disease, (7) the diagnosis of plasmacytoma is made. In one case (7) clinical evidence of typical myeloma of the bone with Bence-Jones protein in the urine appeared eight years later. It is questionable whether such "plasmacytoma" represents a separate entity, as some aver, or not. Jackson and his coworkers (7) do not believe so and regard both myeloma and extramedullary plasmacytoma as different manifestations of a generalized neoplastic disorder of the lymphatic system. The matter of classification of plasmacytoma and myeloma is confused by the fact that the plasma cell and the myeloma cell resemble each other so closely, and what appear to be typical instances of myeloma are reported as of the plasma celled type, and reversely. Whether such a distinction is valid is questionable, because both are derived from the same parent cell—the lymphoid type. There are undoubted plasmacytomata that are extraosseous and remain extraosseous. These have been recently reviewed by Hellwig (8). The extramedullary myelomatous invasion of parenchymatous organs, for instance the liver, spleen and kidneys, associated with an unusual invasion of the circulating blood with plasma cells creates another variant that has been termed "plasma cell leukemia" (9). Most of the reported cases of "plasma cell leukemia" are associated with myeloma of the bone, Bence-Jones proteinuria, and hyperproteinemia, and many are accompanied by plasma or myeloid infiltration of the parenchymatous organs. To call such cases plasma cell leukemia is entirely a matter of definition of the term leukemia. Piney and Reach (11) go so far as to divide myeloma into the leukemic and aleukemic types. Rubinstein (10) postulates that myeloma bears the same relation to plasma cell leukemia as lymphosarcoma to lymphatic leukemia. Observers have reported a host of other variants in respect to the topography and distribution of the myelomatous lesions, the invasion of the blood stream by plasma cells and the presence or absence of Bence-Jones protein in the urine, and have attempted thereby to define separate disease entities; but from the strictly morphological and especially biological point of view, these variants represent one and the same disease, namely myeloma.

Blood changes in multiple myeloma. Aside from a progressive secondary anemia which may be very severe, the most dramatic change when it occurs, is an invasion of the peripheral blood with young leucocytes, mostly plasma cells and myelocytes. We have already referred to the occasional invasion of such an unusual percentage and number of these cells as to resemble leukemia. In one case (12) there were 60,000 cells of which 65 per cent were plasma cells. In another (11) there were 23,000 cells with 16 per cent plasma cells, and 8 per cent myelocytes. Patek and Castle (9) report a case with 50,000 leucocytes of which 33 per cent were plasma cells. Most of such reports represent counts made in the terminal phases. When counts are made serially from the early to the terminal phases, there is as a rule a progressive rise both in number and percentage of

the young forms. Thus Rubinstein (10) reports a rise in the total white blood cell count from 6,000 to 26,000 and a percentage increase of plasma cells from 0.5 to 38 per cent. However, plasma cells may never appear in the blood at any stage, even when there is a pronounced myeloid invasion of the parenchymatous organs as in the case of Churg and Gordon (13). The cause of the variable invasion of the peripheral blood is not clear.

A hyperproteinemia of 9 mgm. per cent or more is found in most of the reported cases. In one case a level of 17.58 mgm. per cent of plasma protein was determined (14), and levels of 12 mgm. per cent are common. Statistics on the incidence of hyperproteinemia in myeloma are almost valueless: first, because very few early cases have been reported; second, because of the paucity of serial determinations; third, because little consideration has been given to the fact that the protein level may be modified by other factors, notably, protein starvation, cachexia and the loss of protein in the urine; and fourth, because a case with a normal protein level or a hypoproteinemia is less likely to be reported. An average general incidence may be gauged by reports of groups of cases by one observer. Thus Magnus-Levy (15) in 5 cases noted a hyperproteinemia in 3; Feller and Fowler (16) in 10 cases noted it in 3; but even in these, the incidence would probably be modified by the above considerations. This will be discussed more fully later. In some early reports (17, 18, 19) the hyperproteinemia was ascribed entirely to an increase of Bence-Jones protein in the blood, but the observers' technique is open to criticism, inasmuch as it did not adequately differentiate between Bence-Jones protein and euglobulin; moreover there is, as yet, no available method of estimating the quantity of Bence-Jones protein in the blood except roughly. With more refined methods, especially by fractionization, ultra centrifugation and precipitation methods, it has been fairly well determined that the concentration of Bence-Jones blood protein is only a small portion of the total (20, 21, 22, 15). All observers agree that with rare exceptions, the largest increments in producing the hyperproteinemia of myeloma are the globulins, especially the euglobulin fraction. In exceptional instances, it is the pseudoglobulin i. (23); in addition, minor protein increments may be present, pseudoglobulin ii, fibrinogen (24) and some unclassified proteins (23). The hyperglobulinemia and the occasional high fibrinogen content is responsible for the positive formol-gel reaction and autoagglutination so commonly observed in myeloma. Hyperglobulinemia is not distinctive of myeloma, since it occurs in most instances (aside from hemoconcentration) in which a hyperproteinemia occurs; for instance, in lymphogranuloma venereum, and in kala azar; also in all such conditions, the albumen fraction is decreased; in consequence there is a reversal in the albumen-globulin ratio. The cause for the development of hyperproteinemia in myeloma is not known. It has been suggested (25) that the blood Bence-Jones protein acts as a foreign protein, causing a rise in globulins similar to that occurring after injecting foreign protein (26). This would only be possible provided Bence-Jones protein in the blood was always accompanied by a hyperproteinemia. Apparently this does not always hold true. In one case (27) apparently large quantities of Bence-Jones protein were present in the

blood and for a period of at least 5 months, but the blood proteins remained consistently normal.

There appears to be no relation between hyperproteinemia or hyperglobulinemia, and the presence of Bence-Jones protein in the urine (23, 21, 24).

The hyperglobulinemia may be the explanation, in part at least, for the local and generalized amyloidosis that is sometimes associated with myeloma (28, 24, 29) since there is evidence (30, 31) both clinical and experimental that hyperglobulinemia frequently precedes the deposition of amyloid.

Bence-Jones protein in urine and blood. Our incomplete knowledge of the biology of myeloma is reflected in the paucity of data concerning the time relations in the incidence of both Bence-Jones proteinuria and Bence-Jones proteinemia in myeloma.

Although the quantity of Bence-Jones protein in the urine is slightly modified by the protein content of the diet (15) it has been fairly established by precipitation tests and by metabolic methods that Bence-Jones protein is entirely endogenous in origin (32, 33, 34, 35) and represents a substance manufactured by the myelomatous tissue. Fleisher (36) and Meyler (37) found Bence-Jones protein in normal marrow. If this is confirmed, the conception that Bence-Jones protein arises from the neoplastic myelomatous tissue would be considerably fortified. The incidence of Bence-Jones proteinuria in myeloma has been variously estimated; 65 percent according to Geschichter and Copeland (38) and 73 percent according to Magnus-Levy (15). These incidences as in the case of hyperproteinemia, are probably specious; first, because the method of determination is faulty. This is particularly evident in cases in which there is a large admixture of serum protein in the urine. Second, because it has been shown by Miller and Sweet (39) that when a urine containing protein is allowed to stand 8 to 24 hours, a reaction simulating that of Bence-Jones protein may be obtained; and third, because the presence or absence of Bence-Jones proteinuria depends to a certain extent on the stage of the disease. In two cases that I have observed, Bence-Jones proteinuria was absent, (in one case for nearly a year) although the diagnosis of myeloma was established in both. In both instances Bence-Jones proteinuria developed subsequently. Nevertheless there is little doubt that Bence-Jones proteinuria may be absent throughout the course of the malady, despite the fact that the blood contained considerable amounts of Bence-Jones protein (27). Magnus-Levy (15) found that the longer the duration of the disease the greater the likelihood of its presence. The reason for its absence in some instances is not clear, because the molecular weight of Bence-Jones protein is about 35,000 (40) as compared to that of serum albumen which is 67,500, so that one would expect it to pass through the glomerular capillaries (40). It has been suggested that in such instances, the Bence-Jones protein is in the form of some complex, perhaps in combination with another protein making it of larger size (20). Hopkins and Savory (36) have shown that other factors aside from more permeability, condition the passage of Bence-Jones protein from the blood into the urine. These are, among others, the acid and salt concentration of the media. We have already remarked that Bence-Jones

proteinuria is frequently associated with a serum albumen proteinuria. Sometimes only serum albumen is present (41). Exceptionally neither serum albumen or Bence-Jones proteinuria occurs although Bence-Jones proteinemia is demonstrated (23). These relations are poorly understood, but unquestionably time factors must be considered as well. One might assume, in some cases at least, that the constant passage of Bence-Jones protein in the urine may injure the kidney sufficiently as to permit the escape of serum protein into the urine. There is suggestive evidence therefore. In one case under my observation, Bence-Jones protein was the only protein found in the urine in the early phase. Terminally, larger quantities of serum protein were additionally excreted. Further evidence is afforded by the well controlled experiments of Forbus and his collaborators (42). Under normal circumstances, the injection of pure Bence-Jones protein into animals, if the dose is large enough, leads to a rapid excretion of the protein (40). Forbus and his collaboraters (42) injected large amounts over a prolonged period and produced a mild form of the characteristic lesion described by Thannhauser and Krauss (43), and Bell (41) in myeloma, namely, a plugging of renal tubules with casts of a peculiar almost crystalline structure, consisting of precipitated globulins. This is the lesion that contributes largely to the renal insufficiency so frequently reported in myeloma. It is interesting to note that these animals persistently voided serum albumen, even when no Bence-Jones protein was passed. The incidence of such a sequence in human myeloma cannot be judged from reported cases, because almost all represent static or almost static observations. One may conceive that if under such circumstances the amount of serum protein is sufficiently large and voided over a protracted period, that a hyperproteinemia might be restored to a normal serum protein content or even to a hypoproteinemia. In a tabulation that I made of reports in which the amount and partition of serum proteins are given together with the approximately quantitative tests for both albumen and Bence-Jones proteinuria, it appears that by and large, the highest levels of serum protein are associated with none or little albumen proteinuria, while the lower levels of serum protein are associated with a more abundant albumen proteinuria.

There is a broad correspondence between the non-protein nitrogen figures in the blood and the total blood serum. The higher the non protein nitrogen the lower the total blood serum and vice versa. However, the correspondence is by no means consistent, and there may be other factors in myeloma beside urinary loss that lower the serum protein; for instance, cachexia and protein starvation. The excretion of Bence-Jones protein apparently has little effect on the hyperproteinemia, which is to be expected, considering that it is an endogenous product. The study of the biology of myeloma is nicely illustrated in the report of Chester (44), who upon the first examination found a total serum protein of 7.65 mgm. percent of which 4.04 percent was albumen and 3.61 was globulin. One year later the total serum protein was 4.93 mgm. percent of which 3.21 was albumen and 1.72 globulin. During this entire period of observation, the patient passed not only Bence-Jones protein but large quantities of serum albumen in the urine. Magnus-Levy (28) points out that when amyloido-

sis complicates myeloma, large amounts of protein may be additionally lost in the urine.

Bence-Jones proteinemia and its relation to Bence-Jones proteinuria. Clinicians were long puzzled by the curious discrepancy between the high incidence of Bence-Jones proteinuria and the low incidence of Bence-Jones proteinemia. Even when Bence-Jones protein was reported to be present in the blood, the validity of the finding has been questioned because the characteristic precipitation between 45° and 60°C. and its complete solubility at 100°C. did not sufficiently differentiate Bence-Jones protein from euglobulin (20). More modern methods obtained by fractionization, by extraction, solubility curves, ultracentrifugation, and specific precipitation tests (since Bence-Jones protein acts as an antigen) (45, 46) have amply demonstrated its presence not only in the blood but in pleural fluid (47) and the pericardial exudate, but not in the cerebrospinal fluid (48). Further, by the technique of electrophoresis most sera from patients with myeloma reveal characteristic patterns (20, 23), that appear in no other malady; these patterns in part represent Bence-Jones protein, as proven by the observation that Bence-Jones protein isolated from the urine when added to normal serum gives the specific pattern (20, 23). In fact, by the electrophoretic method, a protein, presumably Bence-Jones protein, was detected in the serum, when the fractionization method of Howe, did not reveal it. Moore and his coworkers (20) in their 7 cases of myeloma found a correlation between Bence-Jones proteinuria, even when there is no excretion of Bence-Jones protein in the urine, "the possibility of significant Bence-Jones proteinemia is not excluded, because interaction in the serum may result in the formation of non-filterable substances." In the light of these newer data, the entire problem concerning the incidence of Bence-Jones proteinemia and its relation to Bence-Jones proteinuria will necessitate complete revision. The problem is further complicated by the fact that Bence-Jones protein is not a single substance (45, 49) but two or three substances as determined by precipitation tests; that electrophoresis in myelomatous sera reveals hitherto unclassified proteins (23), and that thus far we have only approximate methods of determining the quantity of these substances.

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ABSTRACTS

Authors' Abstracts of Papers Published Elsewhere by Members of the Mount Sinai Hospital Staff

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

Conservation. M. S. Frank. Hospitals, p. 41, December, 1944.

An economy consciousness can be developed among members of the medical staff as well as among hospital employees. Active committees on economy of both the lay and medical boards can be instrumental in fostering an attitude of conservation. The best way of making the staff conservation conscious, is to invite it to participate actively in the hospital's conservation program. The staff physicians are generally the best judges of the validity of economy measures affecting medical practices. Let the individual doctors help, through a sub-committee of their medical board, and with this help will come education—and conservation.

Less is Lost. M. H. Kreeger. Hospitals, p. 67, December, 1944.

The administrative problem concerning an adequate system to guard the personal property of patients in hospitals is described and definite suggestions made.

Physical Medicine in General Practice. W. Bierman. Paul B. Hoeber, Inc., New York, 1944.

The purpose of this book is to tell the practitioner in general and special fields of medicine how he might use physical measures with others which he employs in his effort to be of greatest service to his patient. Emphasis is placed on the techniques of applications and their physiologic rationale. Numerous original line drawings are used to clarify descriptions of techniques. The scope of the book is indicated by the titles of its chapters, which include: heat and cold; hydrotherapy; climotherapy and spa therapy; visible and infra-red radiation; diathermy; the short wave current; fever therapy; surgical diathermy; galvanic current; ultraviolet radiation; massage; exercise; occupational therapy; the conduct of treatments; diseases of the locomotor system; neurological diseases; cardiovascular diseases; diseases of the digestive system; genito-urinary diseases; gynecological diseases; diseases of the eye, ear, nose and throat; respiratory diseases; and dermatological diseases.

The Need and Demand for Psychiatric Care Among Neuropsychiatric Rejectees and Dischargees. S. W. Ginsburg. Published by the Macy Foundation, 1944.

This paper presents a preliminary statistical analysis of certain aspects of a larger study on "The Needs and Demands for Psychiatric Care Among Neuropsychiatric Rejectees and Dischargees." The outstanding findings presented in this paper were the tremendous disproportion between the number of men who were thought to *need* psychiatric care and those who *wanted* such care and, secondly and perhaps even more important, the appalling lack of suitable facilities for the ambulatory care of men rejected or discharged for psychiatric reasons. A complete report of this study is now in preparation.

A Hitherto Undescribed Form of Alopecia Associated with Erythema and Pruritus. O. L. Levin and H. T. Behrman. Urol. & Cutan. Rev., 48: 486, 1944.

A hitherto undescribed form of alopecia with intense, constant pruritus and erythema of the scalp is presented. This condition occurred in women past the age of fifty. It does

not resemble any of the other forms of alopecia which have been described. The prognosis is uncertain as to the return of hair in the bald patches but relief of the pruritus may be obtained.

The Action of Xanthopterin on Tumor Growth. R. Lewisohn, D. Laszlo, R. Leuchtenberger, and C. Leuchtenberg. Proc. Soc. Exper. Biol. & Med., 56: 155, 1944.

The action of xanthopterin on tumor growth was tested with the aid of the bioassay test. A table is presented which shows that xanthopterin is a strong inhibitor of tumor growth. The tests were performed on Sarcoma 180. The degree of inhibition depends on the dose injected. These results were obtained in 30 experiments in which 124 animals were used. Leukopterin did not cause inhibition of tumor growth, even in a dose 100 times larger than that of xanthopterin. Other experiments showed that leukopterin neutralizes the action of xanthopterin.

Danger Zones for the Ureters in Gynecological Operations and how to Avoid Injuries there. J. Novak. Urol. & Cutan. Rev., 48: 7, 321, 1944.

There are five danger zones where injuries to the ureters can happen in gynecological operations: 1. The crossing of the ureters and the iliac vessels (in operations of large ovarian tumors). 2. The floor of the ovarian fossa (in operations of the adnexa). 3. The posterior leaf of the broad ligament (in operations of intraligamentary tumors). 4. The crossing of the ureter and the uterine artery (in Hysterectomy). 5. The intravesical portion on the ureter (in repair of vesicovaginal fistulas). A thorough knowledge of the anatomy of the ureters, their various anomalies and possible dislocations by scars and tumors, a preliminary exposure of the ureter in the respective danger zone, avoidance on any unnecessary isolation and denudation of the ureter, of unabsorbable ligatures in its vicinity, of any impairment of its wall and vascular supply will prevent ureteric complications.

Thoracic Manifestations of Sarcoidosis. S. S. Bernstein and M. L. Sussman. Radiology, 44: 37, January, 1945.

Twelve cases of proved sarcoidosis have provided the basis for a review of the more frequent thoracic manifestations of the disease which are demonstrable roentgenologically. Chronicity and variable degrees of progression of lesions with a tendency to complete healing are stressed as prominent features. Hilar adenopathy and pulmonary infiltration of strand-like, reticulated, miliary, nodular, and confluent types are found. The recession of hilar adenopathy with extension of parenchymatous infiltrations and, *per contra*, enlargement of the hilar nodes with clearing of pulmonary infiltrations have been demonstrated. Although the roentgen features are somewhat arbitrarily classified into five groups, these divisions are used only for description, as the disease changes constantly, and transition from one form to another is the rule. Involvement of the heart, pericardium, or both is suggested by the changes in the size and shape of the cardiac shadow. The resemblance roentgenologically between pulmonary sarcoidosis and other conditions, particularly tuberculosis, may be so close that a diagnosis from the chest roetgenogram alone is not justified. Biopsy, when possible, is the only satisfactory basis for diagnosis.

An Appraisal of the Results of Surgery in Treatment of Regional Ileitis. J. H. Garlock and B. B. Crohn. J. A. M. A., 127: 205, January, 1945.

The authors report a series of 164 cases of regional ileitis. This is a combined series of cases done at the Mt. Sinai Hospital and elsewhere. Those done at other institutions present the subsequent complications following various types of surgery. The Mt. Sinai Hospital group comprise a series of 137 patients. In this group 57 were treated by ileocolostomy with ileal exclusion. There was no operative mortality. Follow-up studies indicate the recurrence in 6 or 10.5 per cent. There were 45 patients treated by a one-stage ileo-colic resection with 6 postoperative deaths or 13.3 per cent. There were 6 recurrences in the surviving group or a recurrence rate of 15.4 per cent. There were 16 patients treated

by two-stage resection with 2 deaths, a mortality rate of 12.5 per cent. The recurrence rate was 28.6 per cent or 4 cases. There were 19 patients presenting combined ileo-colitis treated by resection with 2 deaths, a mortality of 10.5 per cent, and 3 recurrences in the survivors or 17.6 per cent recurrence rate. The authors, on the basis of this experience, strongly favor the operation of ileo-colostomy with exclusion as the operation of choice because of zero mortality and the lowest recurrence rate.

Rehabilitation and the Returning Veteran. S. W. Ginsburg. Ment. Hyg., 29: 20, January, 1945.

Problems in Psychiatric Rehabilitation. S. W. Ginsburg. Better Times, 26: 24, March, 1945.

These two papers report two aspects of a study which was done for the New York City Committee on Mental Hygiene on the problems of neuropsychiatric rejectees and dischargees. A group of 314 men who had been rejected on neuropsychiatric grounds and of 309 who had been discharged on the same grounds was studied. Of the 314 rejectees, 257 were found to need psychiatric help of some kind and of the 309 dischargees, 235 were found in similar need. Of these, only about 25 per cent wanted such help despite their need for it. These two papers discuss, among other things, some of the reasons why men who "need" psychiatric help do not "want" it. Among these reasons are poor preparation by referring sources; ignorance as to the meaning and importance of psychiatric help, especially the wish to avoid the stigmatization of being a "mental case"; and lack of awareness of the resources for such treatment. The studies also deal with problems of vocational adjustment in these groups and it was found that among the discharged men for instance, almost half were in need of some vocational help. The reports also emphasize the now familiar dearth of psychiatrists and psychiatric resources in the community.

Radiographic Visualization of an Intracerebral Dermoid Cyst. S. W. Gross. J. of Neurosurg., 2: 72, January, 1945.

The author reports the case of a 20 year old soldier who had a convulsion while overseas. A few weeks later he began having headaches for which he was hospitalized. Physical examination and all laboratory tests including an electroencephalogram were normal. The plain x-rays of the skull showed an area of decreased density in the left frontal lobe. A pneumoencephalogram showed a deformity of the left anterior horn and a shift of the entire ventricular system to the right. A left transfrontal craniotomy disclosed a large subcortical mass in the left frontal lobe. The mass proved to be a thin walled cyst containing clear fluid in which many yellowish-white flakes floated. In addition a thick layer of deep yellow material having the consistency of paste was adherent to the wall. Numerous short blond hairs were mixed in the pasty material. The patient had an uneventful recovery and was returned to duty. On histologic examination the lesion proved to be a simple dermoid. This case resembles others reported in the literature except for one unique feature—the lesion was visible in plain x-ray films of the skull appearing as a large ovoid area of decreased density.

Absence of the Optic Nerve in Cyclopia. P. Gruenwald. Anat. Rec., 91: 13, January, 1945.

Observations in cyclopic chick and salamander embryos indicate that in this malformation, as in unilateral microphthalmia of the chick, absence of the optic nerve is not due to primary absence of the optic stalk. The stalk degenerates because the absence of a chorioid fissure prevents the ingrowth of nerve fibers from the retina.

Suggestions for Arranging Collection of Medicina in Nummis. B. Kisch. Bull M. Library A., 33: 80, January, 1945.

For the first time a suggestion is made to subdivide systematically the numismatic field of medical coins and medical medals.

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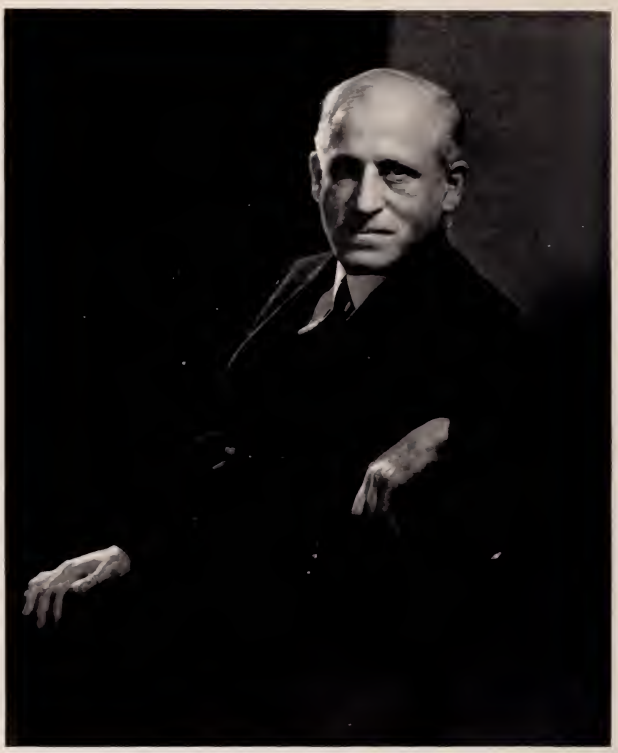

Emanuel Libman

Emanuel Libman, M. D.

August 22, 1872–June 28, 1946

Emanuel Libman died after a brief illness at The Mount Sinai Hospital, the place where he spent the most productive years of his life. Of all its graduates he did so much to build up its structure, to develop its services and its laboratories, to attract promising young men, to cultivate investigation and medical education, that his name will always be identified and associated with that of The Mount Sinai Hospital.

Libman was born in New York City in 1872, at the very onset of that bacteriological era which later stimulated his scientific and clinical interests and in which he was subsequently to play so notable a part. He was graduated from the College of the City of New York and in 1894 from the College of Physicians and Surgeons of Columbia University. While at the old "P. and S." he was deeply impressed by the fine personality and the work of Dr. Francis Delafield, Professor of Medicine at the Medical School. In 1894 Libman entered the Mount Sinai Hospital as an intern and thereafter the Hospital was the chief interest in his crowded life. There he came under the direct teaching of a great diagnostician, Professor Edward G. Janeway, who exerted a permanent influence in shaping Libman's medical career, and in whose memory the Edward Gamaliel Janeway Lectureship was endowed by a friend at Libman's suggestion.

After completing his internship at the Hospital, Libman made his first trip to Europe to supplement his medical education by post-graduate studies in Graz, Berlin, Munich and Vienna. While at the Mount Sinai Hospital he had come to know Dr. Abraham Jacobi and Dr. Henry Koplik, both eminent pediatricians, and he was seriously considering pediatrics as a career. Escherich had discovered the colon bacillus and Libman hoped to learn about infantile diarrheas from him. In a few weeks' work in Escherich's laboratory toward the end of his European tour he discovered and described the streptococcus enteritis, often referred to as the streptococcus Libman. After further post-graduate study in the medical centers of the Continent, he returned to New York and in 1897 was appointed assistant pathologist and some years later associate pathologist

to the Mount Sinai Hospital. The Hospital was at that time located at 67th Street and Lexington Avenue, only three blocks from his home, and there was no time of the day or evening when he might not be found working in the hospital.

His early studies were chiefly bacteriological, although he participated also in the routine pathology and post-mortem examinations. He recognized the importance of autopsies and was zealous in securing permission for such examinations, especially in obscure cases. This was a most productive period in his career, during which he made and published studies in meningococcic, streptococcal, paracolon and pyocyaneus infections, the Widal reaction, Weil's disease, and on the precipitation and whitening of glucose-serum-agar by acid-producing bacteria,—a phenomenon which came to be known as the Libman phenomenon. It was through his great interest in the infections that he developed an unsurpassed technic in blood culture work, and he devoted years of work to this field. Studies of cases in which positive blood cultures were obtained led to many valuable observations and publications on "general infections," a term which he preferred to sepsis or septicemia. He always remembered these cases in great detail and kept their records carefully filed away in the cellar or closets of his home. It was never too late at night for Libman to run down to his cellar to extract some records of streptococcal or paracolon infections to prove a point to a doubting visitor.

His most important blood culture studies were made on patients with otitic infections, particularly lateral sinus thrombosis, and bacterial endocarditis. His observations on otitic infections, presented at the meeting of the International Congress of Otology in Boston in 1912, aroused considerable discussion and established him as an authority in this field.

The combination of his blood culture work and his life-long interest in heart disease, led inevitably to a study of what he first called subacute infective endocarditis, but subsequently named subacute bacterial endocarditis. Because of Libman's clinical description of the disorder, and his thorough study of its bacteriology, pathology, diagnosis, differential diagnosis, prognosis and even treatment, his name will always be associated in the minds of generations of physicians with subacute bacterial endocarditis and bacterial endocarditis in general. It was largely through his

studies, publications, lectures and exhibits that the clinical diagnosis of subacute bacterial endocarditis became a relatively simple matter. His observations on blood cultures in bacterial endocarditis, first reported in 1906 before the Johns Hopkins Hospital Staff, and in more detail with the late Dr. Herbert Celler in 1910, were most thorough and extensive. It is fortunate that he lived long enough to see and participate in the partially successful efforts to arrest or cure the bacteremia of endocarditis by chemotherapy and by surgery (ligation or section of a patent ductus arteriosus).

As a pathologist, Libman devoted himself largely to gross pathology and the correlation of the findings at the post-mortem table with the clinical diagnoses. Many of his earlier observations were reported at meetings of the New York Pathological Society,—the only body in New York City at that time before which scientific studies in the field of pathology, bacteriology, or even physiology could be reported. His discussions at these earlier meetings, and indeed throughout his life, were brilliant and memorable for their wealth of detail, originality, stimulating effect and shrewd, accurate appraisal of the work of others. These brief discussions were not snap opinions, but often important bits of knowledge which had been on his mind for some time before.

Of his pathological studies, his detailed observations on the pathology of subacute bacterial endocarditis were made concomitantly with his bacteriological and clinical studies. Of especial interest to him were those cases which were in the bacteria-free stage, had certain well-defined clinical characteristics, and had associated with them anatomical healing of the endocardial lesions. The healing of bacterial vegetations had already been described by Harbitz and by Osler, but Libman was the first to recognize the group as an entity, and by identifying its clinical and pathological features made possible the diagnosis of the healed stage of bacterial endocarditis during life. In 1923 and 1924, in association with Dr. Benjamin Sacks and as a result of careful gross examination of hearts, he isolated a hitherto undescribed form of endocarditis which he termed "atypical verrucous endocarditis." That this name was too anatomical and too restricted, becomes obvious when one reads the original account of the first published cases: one is impressed by the distinctive clinical picture they described. The dermatologist, Kaposi, and others had previously described cases of acute disseminated lupus

erythematosus with systemic manifestations, but Libman and Sacks were the first to present a fairly complete clinical picture of cases of atypical verrucous endocarditis with and without skin lesions resembling lupus erythematosus. The original clinical description by Libman and Sacks stands and is essentially correct although not all cases have endocarditis. The etiology and nature of this disease is still in doubt and under discussion, and so for the time being it may with propriety be given the patronymic name of the Libman-Sacks disease. Indeed, as late as 1942 Libman received the Silver Medal from the American Medical Association for his exhibit at Atlantic City on "Endocarditis and Libman-Sacks Disease." Equally notable was his extensive exhibit of specimens, drawings and charts of the various types of "Endocarditis" for which he was awarded the Gold Medal by the American Medical Association at its Chicago Meeting in 1912. A similar exhibit on endocarditis was given by invitation at the last International Congress of Medicine held in London in 1913.

Libman entered the Hospital through the gateway of bacteriology, then passed through the portal of pathology into the fertile field of clinical medicine. This he enriched by his brilliance as a diagnostician, by his marvelous memory, by his enthusiasm as a bed-side teacher and by his inspiration as an investigator. He was appointed adjunct physician to the Hospital in 1903, attending physician in 1914 and finally in 1925 he was made consulting physician to The Mount Sinai Hospital; he always retained his active interest in everything pertaining to the Hospital, but especially in laboratory and clinical research work, in post-graduate medical education and in internal medicine. He was steeped in medicine throughout his life, but internal medicine, especially diagnosis, was always his primary objective. Like Janeway, he was gifted with a remarkable memory, and many of his bits of wizardry in diagnosis were based on his recollection of the solution of similar problems in his vast previous experience. His method of diagnosis was rarely explained in a systematic way to his hearers, for like Janeway he would merely state—"I have seen this before." His clinical studies were based on correlation of his earlier bacteriological and pathological work with his bedside experience in internal medicine, and these led to his studies in general infections, otitic infections and endocarditis with fever. Less well-known perhaps are his work on lymphosar-

coma of the intestine, his collaboration with Brill and Mandlebaum in two papers on Gaucher's splenomegaly, and his early pathological observations and clinical diagnoses of coronary artery thrombosis, which like many of his other original observations, he mentioned only in casual discussions and failed to publish in full. His work on coronary artery thrombosis alone would have made his reputation. In a brief historical note on coronary artery disease, in which he refers to his own presentation of six clinical cases of coronary thrombosis before the Association of American Physicians in 1912, Dr. James Bryant Herrick of Chicago wrote the following: "The paper was briefly discussed at the time of its presentation by only one person, Dr. Libman. There was no repercussion for six years. It had fallen a dud." Although Libman's first publication on "Some observations on thrombosis of the coronary arteries" did not appear until 1919, it is to be recalled that long before he frequently discussed this subject on ward rounds and in the post-mortem room. He and the group studying with and under him did so much work in the diseases of the circulation that Dr. Welch wrote "I think one may correctly speak of the Mount Sinai School of Cardiologists, of which Libman was the founder and guiding spirit."

Probably his interest in angina pectoris and coronary artery disease led to more extensive observations on pain in all parts of the body. He developed a new and simple test for sensitivity to pain about 1922 and made many studies on susceptibility to pain. Using this test, he classified individuals as sensitive and hyposensitive, and observed that these different types of humans often presented different symptoms when suffering from the same disease. Libman's choice of pain as a subject of study was a happy one: it was in line with his success as a diagnostician which was based chiefly on his intellect and his direct powers of clinical observation without the use of elaborate apparatus.

It will obviously be impossible to recount all of his clinical work, and it may perhaps be misleading to choose isolated fields of his clinical knowledge. His extensive pathological studies, his broad clinical experience, his detective-like quality of clinical observation and correlation, and his marvelous memory formed the basis of the depth and universality of his clinical wisdom. Many of his colleagues were wont to consult him on questions in the history and literature of medicine, and he seldom failed them. If he did not

have the required information at his fingers' tips, he would rapidly consult his elaborate index and files, and usually would triumphantly flourish the appropriate monograph, reference, reprint, journal or book before his amazed visitor. This erudition and clinical experience made him famous as a consultant, for in addition to his services to the patient, he seldom failed to inform or educate the physician.

It is difficult to say whether his personal contributions to laboratory and clinical research, and his services as a consultant are equal in importance to his promotion of post-graduate education in others. Few have done more in this country to kindle, quicken, stimulate and arouse interest in medicine. He thoroughly believed in continued medical education throughout one's professional life. His more formal efforts in this regard included his inauguration of and procurement of funds for a Committee on Medical Instruction at the Hospital, and his active participation from its incipiency in the activities of the Committee on Medical Education of the New York Academy of Medicine. He was a leading spirit of the latter Committee until the last year of his life, when he reluctantly withdrew because of his failing health. One of the most successful post-graduate teaching ventures was the Graduate Fortnight of the Academy in 1931 of which Libman was the chairman and organizer. This was later mentioned by Dr. Welch who wrote "I doubt if there has ever before been assembled such an instructive and comprehensive exhibit of the cardiovascular system in all its aspects, anatomical, physiological, pathological, bacteriological and clinical as that brought together under the supervision of Libman to illustrate the courses of teaching and demonstrations of the Graduate Fortnight of the New York Academy of Medicine in October, 1931."

He endowed or obtained funds for the Edward Gamaliel Janeway, and the William Henry Welch lectureships at the Hospital in the hope that famous investigators would present their work; also to educate, to stimulate, and to demonstrate new methods to the hospital staff. He established similar lectureships in honor of Hideyo Noguchi at the Johns Hopkins Hospital and of Humphry Davy Rolleston at the Royal College of Physicians in London. It is a matter of particular regret that Libman will not hear the first Lecture to be delivered in London. He was a great friend and benefactor of the Hebrew University in Palestine. Recently he made a

large contribution to the Mayo Memorial Fund. He has left a contingent legacy for the benefit of the Tuskegee Institute of Alabama.

He found happiness in his successful efforts to obtain and endow fellowships, to encourage and assist worthy younger physicians in obtaining post-graduate education at home or abroad, or in the pursuit of scientific research. The Libman Fellowship Fund was established for this purpose by a number of Libman's friends; the Celler Fellowship Fund was created largely through his efforts and has been administered essentially according to his recommendation. More recently the Dazian Foundation for Medical Research was established by a former patient and friend as a token of appreciation of Libman, for his work in behalf of medical education; it has been used primarily to provide post-graduate medical education and to support research. During the War it provided fellowships for Latin-American doctors wishing to pursue research in this country. On October 21, 1946, the publisher of Magazine Digest presented The Merit Award for Public Service and Achievement to the Members of the Board of the Dazian Foundation, which was headed by Emanuel Libman. He was of inestimable assistance to young physicians planning to go abroad for post-graduate study, because of his personal friendship and contacts with leaders of medicine in foreign countries, and because of his knowledge and his critical evaluation of work being done at the various institutions. His personal introductions often opened the doors of opportunities not otherwise available. His preparation of a young physician for a European trip was no casual occasion. Throughout an evening and late into the night and early morning he paced back and forth and dictated at great speed, with occasional reference to a card index, but usually from memory, the names, addresses and telephone numbers of professors to be visited in the itinerary from Hamburg to Berlin, to Dresden and Vienna, with personal descriptions and characterizations, accounts of their work, their prejudices and their special interests, with digressions here and there on bacteriology, pathology and clinical medicine, and an occasional interlude of listening to a gramophone record.

Libman's acquaintance of and friendships with the leaders of medicine were national and international. Among the older friends were Escherich, Rolleston and Thomas Lewis, and William Osler,

William Henry Welch and William Mayo whom he referred to as the Three Williams. Libman was a true hero worshipper. One specific example of this was his discovery of the forgotten and long neglected grave in Jaffa of the great Thomas Hodgkin, who had died of dysentery in Palestine while accompanying Sir Moses Montefiore on one of their travels together. Libman not only found the grave with the obelisk erected by Montefiore, but on May 5, 1927 memorialized Hodgkin in a splendid address and had a wreath placed upon the grave.

The finest tribute to Libman is the "Introduction" by his great friend, Dr. William Henry Welch, to the Libman Anniversary Volumes. This is a perfect tribute, but it is necessarily incomplete, and it is to be hoped that a more complete biography will be undertaken as a labor of love. At least some steps should be taken to collect, utilize and record the material of unpublished work which he gathered in many years of great activity. But all his published and the possible posthumous appearance of other work, will not give a real picture of Libman. Personally he was an inspiration, a guide and a leader to a host of his fellow-workers and to several generations of younger pupils who eagerly gathered around this abrupt, swift-moving, dynamic and enthusiastic physician. He worked indefatigably and at all hours, and he impelled all those about him to work with equal fervor. For many years at the Hospital he carefully collected, prepared, indexed and filed away pathological specimens which he used for teaching and which he demonstrated to many prominent physicians who visited the Hospital. A memorable picture could be made of an evening and night with Libman as he and his coterie of pupils carried jars of specimens back and forth, climbing ladders to set them on shelves, just as in later years they carried books, journals and reprints up and down the stairs of his home in order to abstract, discuss and file the knowledge thus obtained.

Very little of his personal life was left for fields other than the realm of medicine. He was a lover of music; in his youth he played the piano with facility, and even in recent years he could sometimes be persuaded to play his favorite Strauss waltzes. But he preferred to listen to symphonic music and he accumulated a large collection of recorded symphonic music which he played with and without provocation. He was mercurial, had a great sense of hu-

mor, and was a famous raconteur, who kept his audience in roars of laughter as he told story after story of his experiences in consulting practice with doctors and with patients. Those of us who knew him well will always revere him for his humanitarianism, his inspiration and his many thoughtful kindnesses.

In retrospect if one analyzes Libman's career, it is clear that it was the influence of Abraham Jacobi and Henry Koplik that led him to study under Theodor Escherich of Graz and incidentally to become for the time being a bacteriologist. Through his laboratory training and his ambition to follow the example of distinguished diagnosticians, such as Delafield, Janeway and Osler, he saw the great value of correlating post-mortem findings with clinical bedside observations in the wards. For a long time he cultivated productively both fields,—the laboratory work and internal medicine,—and gradually attained his objective of becoming an internist and diagnostician of the first rank. He taught himself much, recognizing the great importance of the fundamental sciences related to medicine, and saw to it time and again that the younger men received basic training previous to their entrance into the more fascinating field of clinical medicine. In this way he became deeply interested in post-graduate medical education, both in this country and abroad. With his colorful personality, quick, keen mind and versatility he was always a great inspiration to everyone who came to know and appreciate his unique qualities. Like Thomas Hodgkin he was "a man distinguished alike for scientific attainments, medical skill and self-sacrificing philanthropy."

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RADICAL SURGICAL THERAPY FOR CARCINOMA OF THE COLON AND RECTUM INVOLVING ADJACENT VISCERA*

AMEIL GLASS, M.D. AND JOHN H. GARLOCK, M.D.

Although it is well-known that carcinoma of the rectum and colon is usually a slowly growing neoplasm and ample opportunity is afforded for diagnosis in the early stages, it is unfortunately true that about 30 per cent of all reported cases are inoperable when these patients finally present themselves for treatment. In order to salvage some of this group attempts have been made by many surgeons to broaden the indications for resection with the result that cases which have contiguous involvement of adjacent viscera without peritoneal or liver metastases, are frequently subjected to surgery of a more radical type than has been practiced heretofore. These resections may often seem formidable but when it is realized that no other treatment is available, the risk should be taken.

The purpose of this paper is to present several instances of radical resection of rectal and colonic carcinoma involving adjacent viscera and to show the practicability of such procedures. It seems to us that the obvious increased risk should not deter the surgeon from embarking upon an operation of such magnitude. We have been impressed by the relatively low morbidity and mortality and the long survival of many of these patients.

Of approximately 500 cases of rectal and colonic carcinoma operated upon on this service in the past 5 years, there were 13 instances of radical resection for involved adjacent viscera. Of these, 6 were carcinoma of rectum and colon with involvement of utérus and vagina, 2 were tumors involving the bladder in male patients, 1 involved the stomach, 1 was a carcinoma of the caecum involving the abdominal wall with a large fungating cutaneous tumor, 1 was a fungating lesion involving the left parasacral tissues and ureter and 2 involved adjacent loops of ileum.

In this group of 13 patients there were two postoperative deaths, one due to localized peritonitis and bronchopneumonia and the other to peritonitis resulting from retraction of the colostomy limb into the abdomen 3 days after operation. Although the latter was an avoidable death it cannot be excluded in calculating the operative mortality, which was 15 per cent. Although this is considerably higher than the mortality following uncomplicated cases, it is not too prohibitive. Both deaths were in cases involving the uterus.

Of the survivors, 1 died of recurrence 1 year later, one is alive and well 5 years later and 9 are alive and doing well on the average of 18 months after operation.

Judged by the two basic criteria, postoperative mortality and period of survival, radical surgery is practicable and should not be denied a patient who is otherwise doomed. From the point of view of a comfortable existence, radical surgery has been a boon in that the complicating factors resulting from involvement of the uterus, bladder, vagina and stomach have been removed. In such

* Presented before the Surgical Section of the New York Academy of Medicine, December 1945.

cases, a proximal diverting colostomy alone does not obviate these complicating factors.

Two cases in which the uterus was removed and 1 case in which part of the bladder was excised because of suspected carcinomatous involvement showed, on pathological examination, that the process in the uterus and bladder was inflammatory and not carcinomatous. The lesion, though apparently involving other viscera, was actually limited to the bowel and resectable. The indication for radical surgery is all the greater in these cases because the results should be better than with cases with carcinomatous invasion.

Management of Gynecological Complications. If the primary lesion is in the colon and an obstructive resection is practicable, the uterus with its appendages is removed completely and brought out in one mass with the colonic tumor. After excising the proper amount of mesentery, the two limbs of the bowel are sewed together and the diseased segment excised between clamps. The subsequent management is the same as an uncomplicated obstructive resection.

If the primary lesion is in the rectum, a one-stage abdomino-perineal resection or a two-stage operation may be done. In both procedures, a total hysterectomy is performed, burying the uterus together with the bowel under the newly formed pelvic peritoneal diaphragm and removed with the rectal segment through the posterior incision. When the vagina is involved along with the uterus, it must be resected and reconstructed at the same time, or at a later date.

When there is involvement of the posterior wall of the vagina alone, the segment of rectum bearing the tumor together with the vaginal wall may be removed through a posterior approach. This follows a first stage sigmoid colostomy. This is the operation described originally by Lockhardt-Mummery. The elliptical incision in the vagina is carried around the entire rectum removing the levator ani muscles and entering the peritoneal cavity through the cul-de-sac in order to mobilize and sever the bowel in the pelvis. After closing the proximal end of the bowel, the pelvic peritoneum is sutured and the wound is packed open. In one case of this type there was insufficient vaginal mucosa to form a posterior wall. The raw area over the sacrum was soon filled in with granulation tissue which was subsequently lined with mucous membrane. Four months later the patient had a normal sized vagina whose posterior wall was the sacrum.

Management of Bladder Involvement. If the base of the bladder is involved by rectal carcinoma, a resection is impossible without destroying the urethra and ureteral openings. If, however, the posterior wall or dome is involved, part of the bladder may be resected. The wall is resutured in two layers and an indwelling catheter and an extraperitoneal suprapubic tube inserted for bladder drainage. A cigarette drain is placed in the region of the sutured bladder wall. The colonic or rectal tumor involving the bladder is removed either by an obstructive resection or an abdomino-perineal operation, as indicated.

The remaining cases required no special management. The case of carcinoma of the rectum involving the lateral sacral tissues and left ureter in a fungating mass was interesting from the standpoint of the urinary complication which followed. Excision of the pelvic ureter and the carcinoma of the rectum, with

ligation of the proximal end was followed by a urinary fistula requiring subsequent nephrectomy. The patient is well 1½ years after operation. The patient with carcinoma of the splenic flexure involvlng the stomach and the formation of a gastro-colic fistula was treated by partial gastrectomy, splenectomy and resection of the colon. She has remained well for 2½ years.

In 2 instances, adjacent loops of jejunum were involved in the carcinomatous process. The loops were excised *en masse* with the colonic neoplasm. Recovery was uneventful in each instance.

The patient with carcinoma of the caecum, originally thought to have appendicitis and operated upon at another hospital, developed a huge fungating abdominal wall tumor and was denied operation at that hospital because of the extent of the lesion. A wide block excision of the abdominal wall and ileocolic resection in one stage was followed by an unexpectedly smooth recovery. It is now about 8 months after operation and the patient is doing very well.

SUMMARY

1. Radical surgery for carcinoma of the rectum and colon involving adjacent viscera is practicable because the mortality is low, the survival period is surprisingly long and the patient is saved the complications incident to the spread of the growth to these adjacent viscera.

2. It should be emphasized that what appears to be neoplastic involvement at the time of the operation may subsequently, on histological examination, prove to be only an inflammatory process.

LOBAR PULMONARY CARCINOMA*

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From the Surgical Service of Dr. Harold Neuhof

The following case is of interest because it not only substantiates some of our conceptions regarding circumscribed pulmonary carcinoma but it also negates some of the commonly held principles regarding indications for operation. In addition, it illustrates the use of thoracoscopy to determine operability.

History. (Adm. # 537953) L. M. a white housewife, 49 years of age, was admitted to the Mount Sinai Hospital on August 8, 1945, complaining of pain in the left posterior chest for five months and shortness of breath for four weeks. On further questioning, it was elicited that she had had pulmonary symptoms for the past four years.

Four years before admission the patient developed a productive cough, with expectoration of approximately 60 cc. of mucoid sputum which contained blood on numerous occasions. X-ray examination of the chest at that time disclosed no abnormalities. During this period she continued to have a cough productive of blood-streaked sputum. Because she had felt exceptionally well and had not lost any weight, she did not seek further medical care. Occasionally the coughing would be spasmodic, and initiate vomiting. The shortness of breath, which began approximately four weeks before admission caused the patient to consult a physician who found fluid in her left chest. The remainder of her history was irrelevant.

Examination. Physical examination, upon admission, revealed dullness and diminished breath sounds over the base of the left posterior chest, slight cyanosis and dyspnea, and early clubbing of the fingers.

Laboratory data. The sedimentation rate was 25 mm. in one hour. Hemoglobin was 93 per cent; white blood cell count was 9600 with a normal differential. Blood urea nitrogen was 13 mgm. per cent and blood sugar, 90 mgm. per cent. Electrocardiogram showed no abnormalities. A sputum culture revealed Streptococcus hemolyticus B and Streptococcus viridans. Numerous sputa were negative for tubercle bacilli. Mantoux test was negative in dilution of 1–10,000. X-ray examination on admission showed "A homogeneous density occupying the lower one half of the left chest. The upper border of the density appears lobulated suggesting the presence of a neoplasm. It is impossible to determine from this examination alone whether or not there is an associated effusion. The density appears to be situated posteriorly." (fig. 1).

Course. On August 10, 825 cc. of cloudy, reddish yellow fluid was aspirated from the left chest. The fluid had a specific gravity of 1.024, contained many red blood cells, 10 per cent of which were crenated. The fluid clotted spontaneously. Culture yielded no bacterial growth, and examination for tumor cells was negative.

On August 16, in preparation for bronchoscopy, she was given morphine and became comatose, due to a sensitivity to the drug. She was revived with stimulants. On August 22, 500 cc. of pleural fluid was aspirated for the second time. Again no tumor cells were found.

It was felt that the patient had a pulmonary carcinoma and it was decided to perform a thoracoscopy. With this minor procedure, the condition of the pleural cavity could be determined, and, if possible, a specimen of tissue obtained in order to substantiate the clinical diagnosis. On August 31, 600 cc. of pleural fluid was aspirated, and air replaced into the pleural cavity. Thoracoscopy revealed the following: "The parietal pleura is

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normal as far as can be seen. There is a puckering lesion in the lower lobe with bluish discoloration and what appears to be scarring. There are no nodules to be seen on either the visceral or parietal pleura. There is no lesion that can be biopsied. The tumor is entirely confined to the lung and is not attached to the chest wall. Exploration is indicated."

On September 6, bronchoscopy was performed, without preoperative sedation. The paravertebral division of the left lower lobe was found to be partially stenosed by thickening of the mucosa and extrinsic pressure. A biopsy was performed, and the specimen was reported as irregular mucous cells suggestive of carcinoma but too small for a definite diagnosis.

Because of the patient's excellent general condition, and in spite of the presence of hemorrhagic pleural fluid, exploratory thoracotomy was decided upon. The vital capacity was 1300 cc. Penicillin was given prophylactically and preoperatively. On September 26, under endotracheal, ethylene-ether anaesthesia, exploration was performed.

The left hemithorax was opened through a posterolateral incision in the seventh intercostal space. A considerable amount of hemorrhagic fluid was evacuated from the pleural

FIG. 1. Large lobulated shadow occupying the lower half of the left side of chest

cavity. The lower lobe was found to be the seat of a massive, round, circumscribed tumor which had replaced practically all of the pulmonary parenchyma of the lobe. The tumor was freely movable, being attached to the thoracic cage by a few filmy adhesions. There was no evidence of any tumor implants on the parietal pleura. There were numerous hilar nodes which were soft, anthracotic, apparently uninvolved. No involved mediastinal nodes were to be found.

Because of the character of the tumor and the absence of involvement of hilar and mediastinal nodes, lobectomy was performed. The artery and vein to the lower lobe were individually ligated; the main lower lobe bronchus was isolated and cut across. This was closed with a double layer of silk mattress sutures. Underwater drainage was instituted in the ninth intercostal space. The phrenic nerve was crushed, and the wound closed with pericostal, muscle, fascial, and skin sutures.

The postoperative course was uneventful. Penicillin was given intramuscularly for five days. The underwater drainage was discontinued on the fifth day. The postoperative temperature did not rise above 101°F. X-ray examination on the fourteenth postoperative day showed an elevated diaphragm, a reexpanded upper lobe, and a small amount of pleural fluid. The patient was discharged on the fifteenth postoperative day.

The pathological report was as follows: "Specimen consists of a resected left lower lobe. The lung is rigid and firm with some adhesions, predominantly over the diaphragmatic surface and also posteriorly and laterally. There is a small amount of collapsed lung tissue at the periphery both at the apex and especially anteriorly at the base (cardiac lappet). Elsewhere the tissue is extremely firm. It is puckered and depressed posteriorly where a yellow color shines through the surface. Elsewhere the color is irregularly congested and anthracotic. The hilar area of resection shows small anthracotic lymph nodes. The main lower lobe bronchus has been transected and opened and does not appear unusual. The apical branch is not unusual. The posterolateral branch is somewhat narrowed but actual tumor invasion is not recognized. On opening the larger bronchi, no tumor involvement is found. One incision has been made through the middle of the lobe. It shows, at the periphery, a greyish yellow, somewhat glistening fairly dry tumor tissue which is firm and shows some anthracotic and yellow flecking. In the central portion of the mass, predominantly, but extending out into the periphery is firm yellow somewhat softer tissue with areas of cheese-like consistency. These areas are irregular in shape and are separated by opalescent firm greyish foci. The section has been carried through additional hilar lymph

FIG. 2. Tumor replacing practically the entire lower lobe

nodes and one demarcated nodule at the hilum appears to be a lymph node involved by tumor" (fig. 2). Microscopic examination revealed that the tumor was a squamous cell carcinoma.

The patient was seen on January 15, 1946, four months after operation. At that time, she was in excellent general condition and had neither cough nor expectoration. X-ray examination of the chest was reported as follows: (fig. 3) "Reexamination of the chest shows no fluid in the pleural cavity. The left upper lobe shows only a horizontal zone of increased density which was present previously and is probably of no clinical significance."

COMMENT

The tumor in this case was undoubtedly of at least four years duration. The normal findings on x-ray examination at the onset can be attributed to the location of the carcinoma in the left lower lobe at that time; a small mass might have been hidden by the heart shadow. We have been able to trace the very slow growth of this type of tumor in a number of other cases in which we were

fortunate enough to obtain previous x-ray films. A number of them have taken as long as two years to reach a diameter of one and one-half inches as seen on the x-ray film. In this case, the x-ray shadow was 4 inches in diameter; the tumor occupied the entire lower half of the hemithorax and had replaced practically all of the pulmonary tissue of the left lower lobe.

In spite of the long duration, and the massive size of the tumor, the patient was in excellent general condition and there were no metastatic hilar or mediastinal nodes to be found at the time of operation. Neuhof and Rabin, in 1934 (1), and again in 1941 (2), called attention to the fact that a high percentage of these circumscribed pulmonary carcinomas do not have metastatic lymph node involvement even late in the course of the disease. It is on this basis that lobectomy is considered sufficiently radical for their surgical removal. This is in contradistinction to the carcinomas of the major bronchi, most of which have

FIG. 3. Follow-up. Elevated diaphragm and expanded upper lobe

early hilar and mediastinal node involvement, and, must therefore be treated by pneumonectomy.

This patient was operated upon only four months ago, and cannot be presented as a cure of carcinoma of the lung. Of especial interest is the fact that a large tumor of four years' duration, with hemorrhagic pleural fluid, was found to be operable. The presence of hemorrhagic pleural fluid complicating pulmonary carcinoma is ordinarily considered as a contraindication to operation because it is due, with rare exceptions, to metastases or direct extension to the pleura. It is possible to find tumor cells in a high percentage of these hemorrhagic fluids. The absence of malignant cells in this case, plus the thoracoscopic findings, pointed to some other causative factor for the sanguineous character of the fluid. The absence of any pleural implants at the time of operation substantiated this view. It is possible that the red blood cells in the pleural fluid were due to exudation from the surface of the tumor which was covered with small capillaries.

Thoracoscopy is a minor procedure which can be used as an aid to clinical diagnosis. Pleural implants can thereby be visualized and a biopsy specimen removed for pathological diagnosis. By this method, the need for a major exploratory thoracotomy may be obviated. In this case, it was of extreme value in determining the absence of any pleural extension in the presence of hemorrhagic pleural fluid.

SUMMARY

A massive circumscribed squamous cell carcinoma (lobar) of the lung of at least four years duration, complicated by hemorrhagic pleural fluid, was found to be operable.

Thoracoscopy was used to determine the presence or absence of pleural metastases.

As operation, no metastatic hilar nor mediastinal nodes were found and lobectomy was performed. The patient has remained well for four months.

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ESSAYS ON THE BIOLOGY OF DISEASE[1]

ELI MOSCHCOWITZ, M.D.

Chapter 17

SPRUE SYNDROME

This syndrome comprises a number of allied disorders that have been variously termed coeliac disease, Gee-Herter disease, Gee-Herter-Thaysen disease, tropical sprue, non-tropical sprue, tropical macrocytic anemia and idiopathic steatorrhea. Any attempt at precise definition between these disorders must necessarily be an artificial one since they largely represent phases or symptom complexes without a precise or uniform etiology or a consistent background in morbid anatomy. From a pathologic-physiological viewpoint there is an extraordinary overlapping. Furthermore, these disorders may give rise through intermediary mechanisms to other symptom complexes in whole or in part, notably pernicious anemia and pellagra. For these reasons, it is highly essential, as Snell (1) points out, to visualize these disorders from the biological rather than the static viewpoint.

In order that we may orient ourselves concerning the conventional nosology of these terms, coeliac disease and Gee-Herter disease are synonymous and represent the sprue syndrome that arises in childhood. The Gee-Herter-Thaysen disease is synonymous with non-tropical sprue and represents the type that occurs in adults. Tropical sprue is identical in every respect to non-tropical sprue; its greater incidence in the tropics is due to the greater incidence of dietary insufficiency consequent upon living in a hot climate. "Idiopathic steatorrhea" is an indifferent term that covers a host of unrelated conditions in which steatorrhea is the main symptom. It is no longer "idiopathic" since it has a number of backgrounds in morbid anatomy, such as pancreatic disease, intestinal stricture and fistulae, obstruction of the intestinal lacteals, and Whipple's intestinal lipodystrophy.

Tropical macrocytic anemia resembles sprue in every particular except for the fact that it is relieved by yeast which contains a substance closely allied to the intrinsic factor of Castle, while sprue requires liver in addition (2). Inasmuch as Miller and Rhoades showed experimentally in swine that, by omitting the extrinsic factor, they produced a loss of intrinsic factor followed by a macrocytic anemia which responded to liver, one has reason to believe that tropical macrocytic anemia represents the early phase of the sprue syndrome, and that the difference between the two is quantitative rather than qualitative. In fact,

[1] This is the seventeenth chapter in a series of essays by Dr. Eli Moschcowitz, in which an attempt will be made to interpret certain forms of chronic disease from the biologic viewpoint, as opposed to the current trend toward rigid classifications implying a concept of disease as a more or less static phenomenon.

According to present plans, these essays will appear in consecutive issues of the Journal of The Mount Sinai Hospital. When the publication of the projected series of essays is completed, the several installments will be assembled and printed as a monograph.—Ed.

the sprue syndrome does not spring into being fully matured. So-called larval or incomplete types have been reported, aside from the macrocytic anemia just described (3, 4, 5). That these larval forms are by no means infrequent is evident from the report of Manson-Bahr and Willoughby (5) who found 22 such instances in 200 cases of sprue. These larval or incomplete types comprise various signs and symptoms; glossitis, weight loss and anemia without intestinal signs, etc. Hanes (4) in reviewing 77 cases of pernicious anemia discovered three that were eventually diagnosed as sprue. Some reports of pernicious anemia without achlorhydria represent in his opinion early forms of sprue.

Etiology and pathological physiology. The etiology of the sprue syndrome was almost entirely conjectural until the fundamental observations of Castle and his coworkers (3) in Porto Rico. They found in fully developed cases a deficiency of the extrinsic factor and in most instances a deficiency of the intrinsic factor. According to Miller and Rhoades (2), the sequence of events appears as follows. As a consequence of the loss of intrinsic factor an inflammatory change in the gastric mucosa occurs as manifested by a glossitis and stomatitis. This first stage is not usually associated with either achlorhydria or anemia. As the disease progresses, atrophy of the gastric mucosa occurs, with resulting achlorhydria and a loss of the hematopoietic activity of the gastric juice; this is followed by anemia, which is usually hyperchromic and macrocytic in type, identical to that of pernicious anemia. Experimentally Miller and Rhoades reproduced the sprue syndrome in swine by administering Goldberger's diet which produces the black tongue disease in dogs characterized by stomatitis, hypochromic anemia, glossitis, diarrhea and prostration. Inasmuch as dogs are not amenable to the experimental production of the sprue syndrome, because the stomach does not contain the hematopoietic agent and the liver is low in the anti-pernicious anemia principle, they employed swine. They produced achlorhydria, macrocytic and microcytic anemia and diarrhea. The achlorhydria preceded the anemia in every instance. Neither the gastric secretion nor the liver contained the anti-anemic principle. The achlorhydria, interestingly enough, persisted in all but one of the animals. At autopsy they found atrophy of the gastrointestinal mucosa.

In sprue, as in pernicious anemia, there is a failure in reaction between the extrinsic and intrinsic principles. In addition, the difficulty of absorption of substances from the intestinal tract resulting from failure of this hematopoietic reaction is probably present in certain instances of both diseases. The essential difference between sprue and pernicious anemia is, that in sprue the achlorhydria is acquired, apparently due to prolonged loss of the extrinsic principle, while in pernicious anemia the evidence is strong that the achlorhydria and the subsequent loss of the intrinsic principle are the result of a familial and genetic factor (6). In both diseases the extrinsic principle acts as the agent that leads to deficiency, for Castle and his coworkers have shown that in most cases of fully developed sprue, liver, especially parenterally administered, is quite as specific as in pernicious anemia. In tropical sprue, the loss of the extrinsic factor is ascribable to the deficient diet of the natives and northerners in the tropics. Ashford (7)

who had an unusually extensive experience in Porto Rico, comments on this fact. The food in tropical climes is insufficient in hematopoietic substances; moreover, the high temperatures subconsciously impel one to choose carbohydrates and fat as the main sustenance. Among the natives, poverty is a factor in such a choice. In non-tropical sprue as well, the history of a previously deficient diet is extremely common (1, 4). The primary loss of the extrinsic principle and later of the intrinsic is paralleled in the corresponding responses to treatment. In the early stages, sprue is often relieved by the vitamin B complex alone; in the later phases liver was necessary. Liver cured even the so-called abortive or incomplete cases, showing that such evidences are not necessarily always early phases of sprue. The presence of acid in the stomach did not necessarily imply that the intrinsic principle was present. Castle and his coworkers found a histamine tested achlorhydria in 31 per cent of all cases, a percentage approximate of that found by Hanes (4). Hanes showed that the acid sometimes returns after treatment, and if hypoacidity was present previously, that the acid rose. Whether the microcytic hypochromic anemia often found in sprue is related to the presence or absence of achlorhydria and indirectly to the presence or absence of the intrinsic factor, is not certain, but the fact that a microcytic hypochromic anemia is practically the rule in coeliac disease of children (8), in whom a complete achlorhydria after histamine never occurs (9, 10), suggests such an association. As far as one can determine, the intrinsic factor has never been determined in the coeliac disease of children. On the other hand, the hypochromic microcytic anemia may represent a phase in the development of the hyperchromic macrocytic variety. Thaysen (11) found that the anemia is of the hyperchromic variety during the active stage of sprue and is hypochromic during the remission. This same phenomenon occurs at times in true pernicious anemia (12, 13). In immediate relatives of patients with pernicious anemia, some show hyperchromic and other hypochromic anemia. Heath (13) was able to convert one type into another by giving either liver or iron over a prolonged period. In pernicious anemia it is sometimes necessary to add iron to liver therapy to fully restore the anemia (3). Castle and his coworkers (3) found similar changes in sprue; after giving liver, the blood picture sometimes changed to the hypochromic type and it was necessary to add iron. Finally, a hypochromic anemia in sprue may, in part, be the result of deficient absorption of hematopoietic substances. Mettier and Minot (14) have shown that such substances are poorly absorbed in the absence of hydrochloric acid in the stomach. The parallelism between sprue and pernicious anemia is further emphasized by the absence of the hematopoietic substance in the liver (3) and the occasional association in sprue of combined sclerosis of the spinal cord (4, 3, 15). Castle and his coworkers found such evidences in 8 of 92 cases of sprue. In summary, this discussion of sprue from the dynamic aspect reveals that a malady, pernicious anemia, whose nosology has heretofore been regarded as more or less sharply defined, has been engrafted, and it is only by a knowledge of the sequence of events that one is enabled to differentiate one from the other. Even the bone marrow in both conditions are identical (3). Of course, it is possible that some

patients may have been individuals with a potential pernicious anemia, and who, under altered dietetic conditions, developed simultaneously the sprue syndrome and pernicious anemia, but this circumstance must be very exceptional, to say the least.

Relation of coeliac disease to the sprue syndrome of adults. Coeliac disease of childhood is clinically identical to that of adults except in two particulars. 1. While hypoacidity is common and achlorhydria less so in coeliac disease, true achlorhydria after histamine never occurs (8, 10). 2. The anemia is nearly always of a hypochromic type (8, 10, 16, 17). These two components, in all probability, are related, inasmuch as all evidence indicates that a hyperchromic megalocytic anemia cannot develop in the absence of a true achlorhydria, in which an absence of intrinsic principle is more likely to occur. Unfortunately, there are no studies available on the determination of the intrinsic principle in coeliac disease of children. Recently, May, McCreary and Blackfan (17) conceiving that coeliac disease represents a deficiency disorder as in adult sprue, administered crude liver extract and the vitamin B complex with striking results, obtained within a period of 3 to 6 weeks of treatment, as shown by a normal absorption of vitamin A, the restitution of a normal glucose tolerance curve and a profound improvement in the general condition and well being of the patients. It seems strange that this concept had not been considered before. They found that either crude liver extract or the vitamin B complex alone was not sufficient. This observation suggests strongly that similar circumstances as regards the relations between the intrinsic and extrinsic principles will be found in coeliac disease. As in adult sprue a frequent history of dietary deficiency is obtained. Coeliac disease usually begins at the end of the first year of life. Although, hyperchromic anemia in coeliac disease of childhood is rare, it does occur. In Parsons' (8) experience, the hyperchromic type was only found in prolonged or neglected cases. That coeliac disease and adult sprue are identical is suggested by the frequent history of transition from one into the other. Time and again in perusing the histories of reported cases of adult sprue, one finds that the disease already began in childhood or even infancy (18, 1, 19, 20, 4, 21, 22) with greater or lesser periods of remission in between.

Gastrointestinal insufficiency as related to the sprue syndrome. The sprue syndrome comprises various other phenomena aside from the changes in gastric secretion and the anemia, that are in a large measure ascribable to deficiency in absorption from the gastrointestinal tract. We refer to the diarrhea, anorexia, emaciation, meterorism and eventually a protuberant abdomen, steatorrhea, hypocalcemia and hypophosphatemia, a flat sugar tolerance curve, a hypoproteinemia, avitaminosis and inability to visualize the gall bladder by oral administration of dye (23). All observers agree that there are no gross postmortem changes in the gastrointestinal tract in the sprue syndrome except thinning of the mucous membranes; and inasmuch as there is complete reversibility with complete restoration of the normal powers of absorption after appropriate treatment, one must conclude that the defective function is directly traceable to the primary etiological defect, namely the failure of interaction between the

extrinsic and intrinsic factor. In other words, this deficiency is an intermediary mechanism which in turn gives rise to the clinical phenomena enumerated above. We will discuss these phenomena in order.

a. *Diarrhea.* Although diarrhea with large foamy and fatty stools are characteristic of sprue, these attributes are not always present (4). b. *Steatorrhea.* In 48 cases of sprue Hanes (24) found that the average amount of fat in the dried stool was 48.5 per cent as compared to the normal which does not exceed more than 15 percent. The steatorrhea is due to defective absorption and is independant of pancreatic insufficiency because in sprue, lipase in the intestinal tract is sufficient. The mechanism of the insufficient absorption of fat is not clear. Barker and Rhoades (25) and Adlersberg and Sobotka (26) found in sprue no increase in blood lipoids after a fatty test meal, and after giving liver parenterally they found a post absorptive blood level which approached the normal. c. *Calcium deficiency.* The low blood calcium in sprue is the result of a number of factors. 1. The steatorrhea results in an excessive formation of fatty acids which combine with the calcium in the intestine to form insoluble soaps which are carried off and thus results a negative calcium balance. 2. The steatorrhea interferes with the absorption of the fat soluble vitamin D. The low calcium, especially of the ionized fraction, leads to occasional tetany, and together with the comparatively low blood phosphorus, leads to osteoporosis in adults, and rickets in children. Due to the poor absorption of phosphorus in sprue, the usual reciprocal relation between blood calcium and phosphorus does not obtain. In Hanes (4) experience, the bony changes in sprue are not as common in tropical climates as in non-tropical, because the increased activity of vitamin D from sunlight neutralizes in a measure the calcium deprivation. In view of the frequent association of tetany, it is interesting to note that Bennet, Hunter and Vaughn (20) found with the slit lamp incipient cataract in many of their cases of sprue. d. *Glucose tolerance curve.* The low glucose tolerance curve is the result of defective intestinal absorption. There is no defect in the utilization of glucose because once it is absorbed or given parenterally, the respiratory quotient is normal (11). Apparently sluggish intestinal mobility is a factor in the absorption of glucose. May and McCreary (27) found in patients with coeliac disease that there was an appreciable rise in blood glucose after giving mecholyl which increased the peristaltic activity. e. *Avitaminosis.* The poor absorptive power of the gastrointestinal tract is reflected in evidences of multiple vitamin deficiency in sprue. That vitamin A is poorly absorbed is attested by numerous observers (4, 26, 28, 17). Inasmuch as the primary defect in sprue is a vitamin B deficiency, tests to prove such a deficiency are not necessary. Scurvy has been occasionally reported in sprue, (15, 1, 4) and vitamin C has been found low in sprue (4). Kirk, Sauter and Hayward (29) found a deficiency of vitamin K in a case of sprue with a pronounced hemorrhagic tendency. f. *Hypoproteinemia.* Despite the fact that nitrogen excretion is only slightly above normal and that amino acids are well absorbed (4) a hypoproteinemia occurs due to both loss of protein and deficient intake and perhaps also to deficient formation, as in pernicious anemia. The hypoproteinemia is manifested in the frequency of

edema. In Snell's (1) series it occurred in 11 of 32 cases. In pancreatogenous steatorrhea there is always a profound loss of nitrogen in the stool (4, 11). g. *Gastrointestinal x-ray pattern in sprue.* Snell and Camp (30) first called attention to a characteristic x-ray pattern in sprue, consisting in delayed mobility and an alteration of the mucosal relief of the small intestine in that the contour is smooth; the valvulae conniventes are obliterated, the barium lies scattered and the colon is dilated. Golden (31) demonstrated the same pattern in pancreatogenous steatorrhea, in avitaminosis without steatorrhea and in pellagra. It is not seen in uncomplicated pernicious anemia. Apparently this pattern is conditioned by a number of factors. First, the diminished intestinal mobility; and second, the steatorrhea itself. Ravdin and his coworkers, (32) showed that in normal individuals the ingestion of olive oil causes an x-ray pattern resembling that found in sprue.

Relation of sprue to pellagra. Pellagra resembles sprue in a number of ways (3, 22, 1, 4, 15, 33, 34). In pellagra, stomatitis, glossitis, diarrhea and loss of weight and prostration are exceedingly common. Achlorhydria according to Sydenstricker (34) is present in most cases, even after histamine. While a hypochromic anemia is the rule, a hyperchromic (34) and megalocytic (35) anemia occurs in a small percentage of cases. Although skin lesions resembling pellagra are occasionally seen in sprue (1, 22, 3) they are not nearly as widespread, or as intense, nor do they lead to ulceration (4). Combined sclerosis is occasionally observed in pellagra (36). In both pellagra and sprue there is atrophy of the mucosa of the gastrointestinal tract. Furthermore, there is a striking parallelism in that both are deficiency diseases. In pellagra the deficiency is the vitamin B complex of which nicotinic acid and riboflavin are the dominating factors (P.P. factor). Sydenstricker has observed pellagra following a high carbohydrate diet in patients with diabetes mellitus who take large doses of insulin. Tbus far the intrinsic principle has not been found missing in pellagra (37, 34, 38). Sydenstricker in a fatal case of pellagra found the hematopoietic principle in the liver. Observations as to whether the intrinsic principle is always present in pellagra are still too few; at all events its presence, as determined thus far at least, probably accounts for the fact that the anemia in pellagra is of the hypochromic type. As in sprue, the acid in the stomach slowly returns after the administration of nicotinic acid; it may take 2 years (34). The similarity between the two diseases is further borne out by the experiments of Miller and Rhoades (2) who produced the syndrome of sprue in swine by giving the Goldberger diet, which is deficient in the P.P. factor, and which in dogs produces the black tongue disease, a malady closely allied to pellagra. Indeed, Harris and Harris (35) report and quote a number of cases of the transition of pellagra into sprue and ultimately with the blood picture of pernicious anemia. Strauss (39) quotes a large number of reported cases of gastrointestinal disorders that were followed by pellagra.

It is apparent that the pathologic physiology of the two diseases overlap to a considerable extent; and whether one or the other disease arises depends in all probability upon the nature of the deficiency, which may even be one that is

still undiscovered, or in a peculiar combination of deficiency principles. It is also by no means improbable that there may be a constitutional factor.

Many of the clinical features of the sprue syndrome are duplicated by other disorders in which the pathologic physiology again overlaps. We refer to pancreatic disease, and stricture and fistulae of the small intestine.

Pancreatic disease. Disease of the pancreas sufficient to completely inhibit the entrance of pancreatic juice into the intestine results in steatorrhea, with wasting, bulemia, diarrhea and a moderate degree of anemia. Snell (1) reports two cases of pancreatic lithiasis in which a macrocytic anemia and a gastrointestinal x-ray pattern like that of sprue was present. Experimentally, (40, 41) by complete exclusion of the pancreatic duct from the intestine or by the artificial production of a pancreatic fistula there is a loss of fat and carbohydrate in the feces and an increased excretion of fecal nitrogen which is related to the increased bulk of the feces. One gains the impression that the syndrome of complete pancreatic insufficiency has not been studied adequately from the clinical aspect. In children, on the other hand, this syndrome appears to have received greater attention, probably because it is more common. There is a malady, only recently described, known as fibrocystic disease of the pancreas, which mimics the sprue syndrome closely (42, 43). It is apparently a congenital and sometimes familial lesion; the symptoms arise in the earliest months of life and in its most common expression the malady is characterized by a failure to gain weight, diarrhea with large foul and fatty stools, infantilism, osteoporosis, usually a low glucose tolerance curve with occasional hypoglycemic symptoms, and a secondary anemia (42). There is a diminished absorption of vitamin A, apparently due to diminished intestinal mobility because it can be relieved by prostigmine (28) or by cascara or posterior pituitary extract (44). Fibrocystic disease of the pancreas can be distinguished from true coeliac disease by the finding of low or absent trypsin in the duodenal content. The determination of amylase and lipase is less reliable (45). Fibrocystic disease of the pancreas represents, in all probability, the majority of cases of "coeliac disease" in children that do not respond to treatment.

Intestinal strictures and fistulas. The occasional close simulation of the sprue syndrome by intestinal stricture was first described by Faber (46). The most complete summary of the subject is that of Barker and Hummel (47) who collected 51 cases including two of their own. The lesions are varied. The small intestine is principally involved, either by a tuberculous or non-tuberculous stricture; the large intestine, less frequently, by a stricture which may be either tuberculous or carcinomatous. Of 18 cases in which an anastomosis was found, the sprue syndrome followed an entero-enterostomy most frequently, less so gastro-colic fistulae or a gastro-jejuno-colic fistula. The clinical expression is characterized by diarrhea, glossitis, occasional icterus and less frequently evidences of cerebrospinal involvement. In 3 cases there was a combined sclerosis. Anemia was present in 100 per cent of all cases; in 39 of the 51 cases it was macrocytic and in 32 hyperchromic in type. An achlorhydria was found in

53 per cent. Of five cases which were tested with histamine, a true achlorhydria was found in 4. The intrinsic principle was tested in 2 cases; it was present in one and absent in the other. In their own two cases, the excellent responses made by administering the extrinsic factor furnished indirect evidence that the intrinsic factor was present. The glucose tolerance curve was determined in 4 cases; in one it was flat, in the other 3 it was practically normal. The bone marrow resembled that of pernicious anemia. While many of the patients responded well to parenteral liver therapy, it obviously could not effect a cure. This was obtained in six cases when the continuity of the intestine was restored by operation. The precise mechanism whereby this syndrome arises in the course of these strictures and anastomoses of the intestine has not been demonstrated, but in all likelihood further investigations will probably show that the mechanism is similar to that which Castle and his coworkers (3) found in sprue, the difference being that in the latter the deficiency was the result of a prolonged lack of the extrinsic principle, while in the former, this principle is not absorbed.

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LIFE'S LATER YEARS

Studies in the Medical History of Old Age

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Part XI*

THE NINETEENTH CENTURY

"When life has been well spent, age is a loss of what it can well spare,—muscular strength, organic instincts, gross bulk and work that belongs to these. But the central wisdom, which was old in infancy, is young at fourscore years, and dropping off obstructions, leaves in happy subjects, the mind purified and wise. I have heard that whoever loves is in no condition old. . . ." *Emerson-Essay on Old Age.*

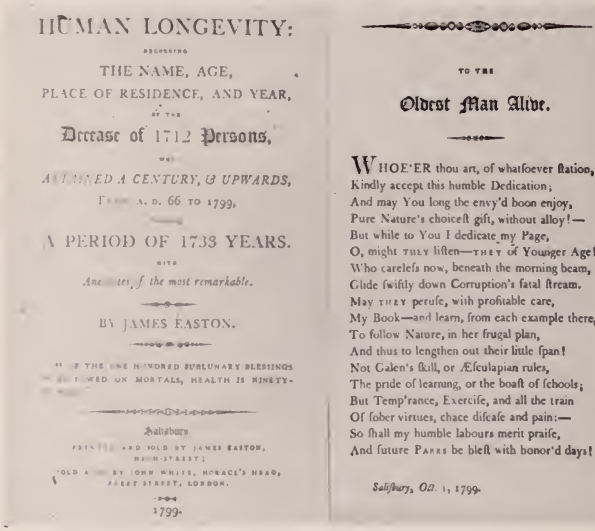
The anatomists of the Renaissance taught physicians to study the structure of the human body. Harvey's great discovery revealed the fundamental truths of bodily function. The observation of structure and function both at the bedside and at the autopsy table led to the recognition of specific disease states, and by means of clinico-pathological correlations made possible the attempt at accurate ante-mortem diagnosis. The work of Morgagni was carried forward vigorously in the 19th century, and aided by stimulating biological concepts and methods of precision, furnished the groundwork for searching studies of the pathogenesis of all types of maladies. These efforts were crowned by the detection of the microscopic living agents of many diseases and finally by the development of methods of specific cure and prevention. These discoveries not only revolutionized medical thinking but altered the way of life of all civilized nations to such a degree that the death rate among children and young adults began to recede measurably. Longer and heathier life was assured to mankind.

In the understanding and the treatment of the aged sick the rapid advances of medicine had broad effects, leading to establishment of sound theoretical viewpoints, more careful observations and to the publishing of at least five major works and innumerable briefer contributions to the problem. The greatest activity is to be noted in the first sixty years of the century. Later the revelations of modern bacteriology and immunology seem to have absorbed the time and interest of all physicians who busied themselves in clinical research. The old profited in no small measure from the improvement in public hygiene, and were the particular beneficiaries of Listerian and aseptic surgery.

The pre-eminence of French medicine in the latter part of the 18th century and the first sixty or seventy years of the 19th is well known, and is to be explained

*This is the eleventh in a series of articles dealing with Studies in the Medical History of Old Age. Upon completion of their publication, the installments will be collected and reprinted in a single volume, constituting one of the Series of Monographs of The Mount Sinai Hospital Press.-Ed.

by the interest of Gallic investigators in fundamental chemical and physical studies as well as their practical applications. Lavoisier's discovery of the role of oxygen in combustion in 1775 and the application of this principle to respiration paved the way for the great physiological schools of Magendie and Claude-Bernard. Even the therapeutic excesses of Broussais and Bouillaud did not prevent these men from advancing medical thinking. The roster of famous French physicians in the early 1800's is in itself impressive, including Laennec (1781–1826), Bayle (1774–1816), Bretonneau (1771–1862), Louis (1787–1872),



HUMAN LONGEVITY:

DESCRIBING

THE NAME, AGE,

PLACE OF RESIDENCE, AND YEAR,

OF THE

Decease of 1712 Persons,

WHO

ATTAINED A CENTURY, & UPWARDS,

FROM A. D. 66 TO 1799.

A PERIOD OF 1733 YEARS.

WITH

Anecdotes of the most remarkable.

BY JAMES EASTON.

"IF THE ONE HUNDRED SUBLUNARY BLESSINGS WERE BESTOWED ON MORTALS, HEALTH IS NINETY-

Salisbury:

PRINTED AND SOLD BY JAMES EASTON, HIGH-STREET;

SOLD ALSO BY JOHN WHITE, HORACE'S HEAD, FLEET STREET, LONDON.

1799.

TO THE

Oldest Man Alive.

WHOE'ER thou art, of whatſoever ſtation,
Kindly accept this humble Dedication;
And may You long the envy'd boon enjoy,
Pure Nature's choiceſt gift, without alloy!—
But while to You I dedicate my Page,
O, might THEY liſten—THEY of Younger Age!
Who careleſs now, beneath the morning beam,
Glide ſwiftly down Corruption's fatal ſtream.
May THEY peruſe, with profitable care,
My Book—and learn, from each example there,
To follow Nature, in her frugal plan,
And thus to lengthen out their little ſpan!
Not Galen's ſkill, or Æſculapian rules,
The pride of learning, or the boaſt of ſchools;
But Temp'rance, Exerciſe, and all the train
Of ſober virtues, chace diſeaſe and pain:—
So ſhall my humble labours merit praiſe,
And future PARES be bleſt with honor'd days!

Salisbury, Oct. 1, 1799.

FIG. 1. Title page and Dedicatory Poem of Easton's curious work on Longevity, which reminds us of the fascination exerted by the centenarian on the popular mind.

Andral (1797–1876), Piorry (1794–1879), Pinel (1745–1826), Corvisart (1755–1821), Cruveilhier (1791–1873), Ricord (1799–1889) and Rayer (1793–1867).

That the Paris physicians devoted so much of their time to the study of the old is due to the fact that two of the city's most active centers of medical research were the Salpêtrière (1) and the Bicêtre (2), both hospices for the aged. They had been established by the decree of Louis XIV in 1656 as parts of the Hôpital-General which comprised, in addition, the institutions of the Pitié, the Réfuge and the Savonnerie. The Sâlpetrière, which derives its name from its previous use as a saltpeter factory, was used for women: prisoners, insane, aged and sick, all being housed under its broad roofs. The Bicêtre served the same mixed

purposes for men. According to Guillain and Mathieu, "recalling the history of the Salpêtrière is to recall the history of three centuries of Paris." "Refuge of thousands of aged, great center of neurology, great center of psychiatry, the Salpêtrière has only become adapted to its actual role by stages. It has seen within its walls the men of the 17th, 18th, 19th and 20th centuries according to their successive conceptions, attempt to resolve the great problems of public and private charity, of aid to the poor and the aged, of the protection of society against the insane and the defective, of the protection of the insane and defective against society; it has seen. . .the creation of scientific psychiatry. The birth

FIG. 2. Interior Court of the Salpêtrière in Paris, with a view of the dome of the chapel in the distance.

and development of French neurology are inseparable from the name of the Salpêtrière" (3).

Since these institutions were built for the housing of three or four thousand inmates each, it can be easily understood that clinical material of great variety was never lacking. The Bicêtre is justly famous as the place where on May 24th, 1798 Philippe Pinel removed the chains from the insane and initiated the humane treatment of the mentally sick. Although his text book of insanity is to-day a medical classic, he also wrote about old age. His remarks on senile asthenia, written in 1812 and published posthumously by his son in 1823, emphasize that this condition is not a clinical entity but one found in a great variety of senile disorders, some of which he discusses briefly (4).

In addition to the easy access to the clinical material of these great institutions for the aged, another factor determining the attitude of French physicians must be pointed out. Marie-François-Xavier Bichat (1771–1802) has been described by Garrison as "the creator of descriptive anatomy" (5) because of his original contributions to this subject. His "*Recherches Physiologiques sur la Vie et la Mort*" (6) although based on the fallacious concept of vitalism, is noteworthy for its discussion of the changes preceding death in old age.

> "*Look at the man who comes to the end of long old age: he dies little by little; his external functions terminate one after another; all his senses close up successively; the ordinary stimuli of sensations strike them without response.*"
>
> "*This is the great difference between death in old age from that which is the effect of a sudden blow. In the first, life begins to fade in all parts of the body, and ceases finally in the heart. Death extends its empire from the circumference to the center. In the second, life is extinguished in the heart, and later in all parts of the body. Death manifests itself from the center to the circumference.*"

Bichat's works were translated into German and English and had a broad stimulating influence, often giving rise to violent controversy.

René-Théophile-Hyacinthe Laennec (1781–1826) touches on all aspects of medicine in his famous "*Traité de l'auscultation médiate*" published in 1819. Here too we find important comments on conditions seen in the aged, one referring to a lung abscess in a woman of 68 years, and another, often quoted, is described under the heading, "Occasional Causes of Tubercles."

> "*The ancients believed that phthisis attacks more particularly individuals between the ages of eighteen and thirty-five; it is true that at this period the disease is most frequently manifest and easiest of recognition. . .However no age is exempt from it. . .It is very common even in advanced old age. I once opened the body of a woman ninety-nine years and some months old, who had died of this disease. Women are more subject to it than men.*" (7)

Among the contributions of French physicians of this period to the hygiene of old age, may be mentioned Tenon (8), Janin (9) and Terrier (10). Guyetant's popular work (11) was composed when the author had experienced 30 years in practice, and in general conforms to the old Arab formula for books designed for lay readers. It is a well written book, with a glossary of the few scientific terms used. He lays special emphasis on the problems of women, pointing out that they live longer than do men. Rostan, one of the celebrated teachers of the Salpêtrière, demonstrated that the so-called "asthma of old age" was due to an organic rather than to a nervous cause (12). He also contributed to the problem of cerebral softening, comparing it with the peripheral gangrene seen commonly in the aged (13). Magendie, the famous physiologist and pharmacologist, demonstrated the changes in the tissues of the lung in the old (14), observations which were later well utilized by Hourmann and Dechambre in their celebrated study of pneumonia in the aged women of the Salpêtriére (15).

This famous clinical and pathological contribution contains many valuable

observations. The authors point out the general dilatation of the bronchial tree in old age and that the mucous membranes of the bronchi are the habitual site of an abundant secretion, a true physiologic bronchorrhea. They describe the different types of chest in their patients, and the auscultatory findings in each. They record respiratory and pulse rates, mentioning pulse frequencies as low as 20 and 30 beats per minute. Pneumonia is discussed from the standpoint of the frequency in the aged, the pathological anatomy, together with the general and special symptomatology. They stress the frequent absence of any expectoration, especially of the blood tinged variety, the absence of dyspnea. The early physical signs are sonorous rales associated with diminished breath sounds. The picture they have drawn of latent pneumonia is famous through its quotation in part by Charcot in his "Lectures on Old Age" (1868). In 1916 this passage was read to the third year students at the College of Physicians and Surgeons of New York by the Professor of Medicine, Dr. Warfield T. Longcope. The present writer, a member of the class, has never forgotten the occasion and has always been aware of his debt to a great teacher.

> "*Finally in some even more obscure cases our old ladies complain neither of weakness nor of malaise. They do not seek admission to the infirmary; no one in their dormitory, neither the nurses nor the attendants nor their neighbors detect any change in their behavior. They arise, make their beds, walk about, eat as usual; then they feel somewhat fatigued, throw themselves on their beds and expire. This is called sudden death from old age at the Salpêtrière. One opens the bodies and finds a large part of the pulmonary parenchyma in suppuration. Remarkable feats of this class take place under our eyes at the infirmary among women admitted originally for diseases entirely remote from the lungs, of which they have been cured.*"

Hourmann and Dechambre also recorded observations on senile ankylosis of the spine (16).

Jean Cruveilhier (1791–1873) the great pathologist, was also a member of the staff of the Salpêtrière and there collected many of the cases which he used so well in his atlas of pathological anatomy where the clinical history of the patient was recorded with the post-mortem findings, beautifully illustrated by large colored plates (17). Prus, working at the Bicêtre, studied the pathological findings in 390 individuals in an effort that "the medicine of old age shall more and more cease to merit the reputation of inutility to which it is condemned by the ignorant and poorly informed". The causes of death classified anatomically were: respiratory, 149; nervous, 101; circulatory, 64; gastro-intestinal, 49; liver and biliary passages, 8; miscellaneous, 19. This study contains much valuable material (18).

Quetelet's (19) anatomical work on the developmental changes, in men and women contained many observations on age changes, especially with reference to weight. His findings were quoted with approval by later writers such as Geist and Charcot. The clinical studies of Beau at the Salpêtrière (20), especially his paper on spleno-hepatic relations (21) represent the best in straightforward bedside medicine. In the latter essay we find the following striking notation:

"In the Salpêtrière infirmary few autopsies are made without there being found a greater or smaller number of calculi in the gall bladder, yet biliary colics are extremely rare at the Salpêtrière."

Another contribution from the same center of the clinical study of the old is that of Neucourt on the heart. Among his conclusions are the following:

"Abnormal sounds arising in the cardiac orifices may exist without affecting its function."

"Some cardiac abnormalities even with very profound alterations in the function of this organ may exist a large number of years without bringing about death." (22)

Gendrin's paper on the influence of age on sickness apparently impressed his contemporaries for it is often quoted with approbation. Like other similar efforts it contrasts infancy and childhood with old age. This writer uses the term *"senile cachexia"* to designate the sum of all the changes which we would to-day ascribe to the aging process itself. Following its introduction by Gendrin the term came into use in France and Germany as a diagnosis, even as a cause of death, corresponding to the use of *"old age"* in English speaking countries for the same purpose (23).

An interesting commentary on the medical thinking in France about the needs of the dependent aged is to be found in two notes published in the Annals of Hygiene. The one concerns a discussion by the eminent physicians Esquirol, Chevallier, Villermé and Parent-Duchatelet on the necessary features of hospitals designed to care for the sick aged (24). The emphasis is laid on low buildings because of the difficulty of the aged in climbing stairs. The second comprises the report of the committee on charitable establishments regarding the question of whether it is better to place aged persons in hospices or to board them out in the country. This discussion properly reaches no definite conclusion, since the same question is still being debated over 100 years later (25).

While the physicians of Paris worked faithfully at the problems presented by their aged patients, a gifted young German, practicing in the obscure village of Ansbach, published in 1839, what Charcot grudgingly admitted was "the first dogmatic treatise that has appeared upon the diseases of old age." Carl Friedrich Canstatt's *"Die Krankheiten des hocheren Alters und ihre Heilung"* (26) was the first attempt at a comprehensive treatment of the subject since Johann Bernhard Fischer's *De senio* in 1754. Before discussing this famous work it will be well to review some of its medical background.

According to Garrison, "up to the year 1850 and well beyond it, most of the advancements in medicine were made by the French" (27). He ascribes the backward position of German science to the prolonged depression resulting from the Napoleonic wars and to the prevalence of many fanciful medico-philosophical cults. In spite of a general tendency to unrestrained speculation on the part of some physicians, sound scientific achievement can be found in the work of such outstanding individuals as Johannes Mueller (1801–58), the distinguished physiologist and teacher, Matthias Schleiden (1804–81) and Theodor Schwann (1810–82), co-discoverers of the cellular structure of plant and animal tissues, Lucas

Schoenlein (1793–1864), founder of modern clinical teaching in Germany and teacher of Canstatt, Carl Rokitansky (1804–78) the noted Viennese pathologist and Jakob Henle (1809–85) the great histologist. It is thus apparent that the triumphs that German medicine achieved in the latter half of the century did not arise *de novo*, but were based on the work of men of the highest ability.

In tracing the work of German physicians on old age, we note the first monograph on the anatomy of the aged by Burkhard Wilhelm Seiler (1779–1843), *Anatomia corporis humani senilis specimen*, which appeared in Latin at Erlangen

FIG. 3. Carl Friedrich Canstatt (1807–1850). (from the Wolfe Collection, Syracuse University, through the courtesy of Dr. H. A. Weiskotten).

in 1800 (28), in a Dutch translation in 1804, and in German in the *Archiv für die Physiologie* in 1805 (29). It is a careful, critical but unoriginal compilation of the knowledge of his day, emphasizing, as Steudel (30) points out, that the anatomical features of the adult are greatly modified in old age and that man is so changed by prolonged functional activity as to become in old age a different being. He recognizes that most old people die of disease rather than old age, and that these disease changes must not be confused with results of the aging process itself. He advocates, in addition to dissection, the use of the microscope and chemical examination of the bodily fluids. He admonishes the physicians connected with homes for the aged to take advantage of the material at their dis-

posal and stresses the necessity for repeated observations before any manifestation be ascribed to old age itself. Here Seiler indicates the progress that had been made since the days when old age was itself considered a disease. An often quoted observation of Seiler is that rigidity is the constant accompaniment of old age (*Rigiditas senectutis perpetua comes*).

The lengthy contribution of C. A. Philites in the year 1809 an old age and senile marasmus is typical of the German medicine of that day since the first half is taken up by a prolonged philosophical discussion (31). On the other hand, he divides life into a period of increment and a period of decrement, a concept that is very close to Canstatt's concept of old age as involution. Philites uses the term senile marasmus to indicate the changes of senescence. Relatively little space is devoted to disease in the aged, but Philites states that in old age every effort must be made to conserve the vital energies.

In the year 1801 the Emperor Joseph Academy of Medicine and Surgery in Vienna offered a prize for the best essay on the diseases of the bladder and ureters in old men, with the exception of stones. For many years no award was made although in 1806 W. J. Schmitt published a work on this subject which apparently was not considered worthy (32). The contribution of Samuel Thomas Soemmering (1755–1830), famous anatomist (33), the first to describe achondroplasia and a prolific writer on a variety of topics, was finally awarded the palm. It is an excellent piece of work, richly annotated with many references to contemporary authors, covering each anatomical feature of the urinary tract except the kidneys. Part of the introduction is worth quoting.

> *"To every physician who busies himself with the thorough study of his science, it should be a personal obligation to learn to know exactly the variations from normal of the anticipated diseases, to trace their remotest causes, their smallest results, and to train himself in the easiest and safest removals of them with unconcern, when he realizes that these maladies become more threatening to himself with the advancing years, and that the highest rulers, the wisest statesmen, cannot escape them, but as sacrifices to them, arouse the compassion of their contemporaries."*

Between the publication of Soemmering's work and the appearance of Canstatt's classic volumes, we find recorded in the Index-Catalogue of the Surgeon-General's office more than twenty Latin treatises devoted to some aspect of old age. With few exceptions none of these works appears to have created much impression on contemporary thinking and writing. During the same period about ten contributions to the subject written in German are to be found. These vary from Loo's paper on the use of drastic purgatives in the aged (34), and Mayer's on the changes in the female genitalia in old age (35), to Kruger's study of the natural healing power at various periods of life (36).

Carl Friedrich Canstatt (1807–1850), one of Schoenlein's most distinguished students, made a lasting impression on German medicine, crowding great accomplishments into a short life. While practicing in the Bavarian village of Anspach, he published his work on old age. Two years later appeared his text book of medicine which was standard for many years, and was re-issued after Canstatt's

death under the editorship of E. H. Henoch. In 1844 he was called to Erlangen as professor of medicine. He is noted also for the journal which he founded in 1841, *Jahresbericht ueber die Fortschritte der gesamten Medizin in allen Laendern*, which was later carried on by Virchow.

The book on old age is divided into two volumes, the first or general part dealing with the anatomy and physiology of old age, and the second, or special part, devoted to the description and treatment of specific diseases. To Canstatt, old age is identical with involution, and he traces the various changes found in every part of the body, emphasizing that there is no rule about the order of their appearance. In his discussion of diseases he separates the essential involutional maladies from those conditions which are seen at all periods of life but are modified by the changes of old age.

Canstatt's book was sparingly admired by Durand-Fardel and Charcot, and at the same time subjected to the criticism that it is not based on careful personal observations, and that it indulges too much in the speculative philosophy so dear to the German mind. Actually these adverse comments are in part justified. Canstatt's clinical experience with old age must have been acquired chiefly during his practice in Anspach, the total population of which could not have equalled the number of old men and women in the Salpêtrière and the Bicêtre where Durand-Fardel and Charcot spent many years, as observed by Steudel. In spite of all shortcomings it is thoroughly modern in spirit, well written and worthy of reading even to-day. Felicitous expressions occur frequently, such as, "the old man dies off while living", which is reminiscent of Bichat, with whose works Canstatt was familiar. He has good understanding of the mental manifestations of old age, commenting that "psychic indifference may show itself in disgust with life and in suicide". His therapy is conservative, and his observations on the dosage of drugs very sound. All in all Canstatt's work set up a standard for all future workers in the field and laid the foundations for a scientific study of aging and disease, since the author does not hesitate to indicate the numerous unsolved problems and constantly urges his readers to fill up these gaps.

Although the merits of Canstatt's work were recognized by German and French physicians, it seems never to have been translated into English. The attention of the leaders in medical thinking in Great Britain was never attracted to disease in the aged as a special object of study. On the other hand the traditions of Sydenham, Heberden, the Hunters, Fothergill, Parry and Jenner had been carried on by a group of physicians whose contributions to general medicine frequently were concerned with diseases common in the old. We need mention only John Cheyne (1777–1836), Robert Adams (1791–1875), Robert Graves (1796–1853), William Stokes (1804–1878), Sir Dominic Corrigan (1802–1880), all of whom advanced the study of heart disease and described important clinical phenomena for the first time. Richard Bright (1789–1858) in his famous "Reports of Medical Cases" (1827) established nephritis as a definite clinical entity by the correlation of urinary findings with the pathology of the kidney, and differentiated between edema of renal and cardiac origin. In Garrison's opinion, "as an ori-

ginal delineator of disease, he ranks next to Laennec" (37). Thomas Addison (1793–1860) with his description of pernicious anemia, Thomas Hodgkin (1798–1866) with his contribution to glandular pathology, and Joseph Hodgson (1788–1869) with his studies of aortic aneurism, all increased the field of medical understanding. James Parkinson (1755–1824) contributed his "Essay on the Shaking Palsy" in 1817, describing the disease which has ever since borne his name.

Aside from Jameson's book (38), the first work of any importance on old age was published in London in 1818 by Sir Anthony Carlisle, the noted surgeon (39). This slender volume entitled "An Essay on the Disorders of Old Age", is written

Fig. 4. Sir Anthony Carlisle (1768–1840)

in epigrammatic style, without any references to other books on the subject. It contains good advice on hygiene, advocates the judicious use of blood-letting, which can only be learned by experience, comes out against emetics for the aged, and is strongly in favor of alkalis for a variety of purposes. He attributes urinary retention to cerebral and bowel diseases, describing the relief from catheterization as temporary and delusive. In general he is opposed to surgery in the aged: "even if the patients prefer the sacrifice of life to the endurance of protracted suffering, still the surgeon should refuse to comply with their improper wishes, and not become a party to homicide".

We recall at this point the publication in 1804 of Sir John Sinclair's four volume compilation, entitled "The Code of Health and Longevity, or a Concise View of

the Principles Calculated for the Preservation of Health and the Attainment of Long Life, being an attempt to prove the practicability of condensing, within a narrow compass, the most material information hitherto accumulated, regarding the most useful arts and sciences, or any particular thereof" (40). In the first volume Sinclair, who also wrote extensively on finance and agriculture, summarizes the best opinions on diet and hygiene; in the subsequent three volumes he reprints extracts from the works of authorities such as Friar Bacon and Lord Bacon, bibliographies on old age and longevity from Ploucquet, as well as personal letters from friends in different parts of the world, including Dr. Benjamin Waterhouse of Cambridge, Massachusetts. This is on the whole a useful book of reference, and the author surely made a brave attempt to relieve others of the necessity of consulting as many books as he himself had to do.

Easton's volume on "Human Longevity" published only a few years before Sinclair's Code of Health, lists all the centenarians known since A.D. 66 (41). It is another illustration of the fascination of the very long-lived for the popular mind, which was pointed out in connection with Thomas Parr. The frontispiece and dedication of this odd work are reproduced in Figure I. Another popular work, "The Economy of Health", was published in 1837 by James Johnson (1777–1845), (42) naval surgeon and Physician Extraordinary to the King. The explanatory subtitle is almost an abstract of its contents.

Marshall Hall (1790–1857) who is noted for his work in neurology, was also the author of a work on the diseases of women (43). Part 3 is entitled, "Of the Disorders Incident to the Middle and Later Periods of Female Life." In Chapter VI he discusses the local diseases resulting from disorder of the general health in the later periods of life, commenting on the frequency of paralytic attacks, which he ascribes to a disordered state of the general health and loaded condition of the large intestines. In the final chapter, "Of the Decline of the Vital Powers in Old Age," three brief pages are devoted to quoting Sir Henry Halford's remarks on "the state of sinking in old age" (44).

A more ambitious effort in the interest of the hygiene of old age is to be found in Barnard Van Oven's "On the Decline of Life in Health and Disease: being an attempt to investigate the causes of longevity and the best means of attaining old age" (45). Written after thirty years in practice, the author points out that no similar volume has been attempted since Hufeland's *Macrobiotik*, 65 years earlier. The "Medical Notes and Reflections" of Henry Holland, published in 1840, has a chapter on the medical treatment of old age (46). J. A. Symonds contributed a carefully thought out article on "Age" to the Todd Cyclopedia of Anatomy and Physiology, 1835–6 (47). P. M. Roget was the author of the section on "Age" in the Cyclopedia of Practical Medicine, in which are described the changes of senescence and a few common diseases. He considered age as the state of transition between maturity and decay. "Spontaneous decay of the body and decline of its powers, invariably attending the lapse of years, arise altogether from causes that are internal and interwoven with the very condition and laws of its existence and are but little influenced by external circumstances" (48).

George Edward Day (1815–1872) was a graduate of Edinburgh and Cambridge,

who later became professor of anatomy at St. Andrews. From his biographer we learn that he was a frequent contributor to medical journals and translated several German text books. It is therefore not surprising to find that in 1848 he published "A Practical Treatise on the Domestic Management and Most Important Diseases of Advanced Life" (49), with a foot-note acknowledging his debt to Canstatt, from whose work he states that he has drawn freely in several parts. Whatever his debt to his German colleague, Day has written the best text book on the subject in English in the whole 19th century, for while others later made single contributions, he remained without rival in his own country until Sir Humphrey Rolleston became interested in old age, more than a half century later. The volume is written in an interesting style, with many references to contemporary English and Continental clinicians, and with many personal case reports.

In the United States the valuable contribution to the study of old age made by Benjamin Rush in 1793 seems to have had but little influence in stimulating his colleagues to similar endeavors (50). The celebrated Dr. Benjamin Waterhouse of Cambridge, Massachusetts, one-time professor of medicine at Harvard University and first to practice vaccination in this country, expressed some views on old age in a letter to Sir John Sinclair.

> "... *During the natural change that takes place between 48 and 50, no particular organ suffers, but a gradual and uniform deterioration supervenes. At this time he first experiences a reluctancy to stoop; he prefers a carriage to riding on horseback, and he finds himself more affected by the weather ... regains his health, with a little diminution of muscular strength, until he turns sixty; then the gravity of age is more strongly marked, and he begins to boast of his age and its prerogatives. This is the result of my observations on others, compared with my own personal experience, which goes no farther than your own, being born in the same year, viz. 1754.*" (51)

In 1815 John Scudder presented as his inaugural dissertation at the College of Physicians and Surgeons in New York City, "On the diseases of old age, as connected with a plethoric state of the system." He stresses the value of blood-letting, quoting the authority of his preceptor, Hosack, as well as Lettsom, Boerhave and Van Swieten. He ascribes gout and palsy to plethora, and reports briefly four cases which he had observed, aged 74, 73, 48 and 34 years, all of whom were helped by phlebotomy (52).

Abel Lawrence Pierson (1794–1853) described in 1829 two cases of disease and dissection in old age (53). He states that the wearing out of organs varies in the individual due to his original formation, his occupation, habits and temperament. Imperfections in the vital organs are not incompatible with vigorous health. The first patient, a well known political figure who had served in the army at Yorktown, died at the age of 84 years after an eleven day illness. Necropsy showed a large left empyema, enlarged prostate, marked sclerosis of the abdominal aorta and iliac vessels. The pericardium was adherent and the heart showed areas of ossification in the myocardium and the semi-lunar valves.

Pierson's second patient was the famous centenarian, Dr. Edward Holyoke of Salem, Massachusetts. The complete story of this aged physician is also to be found in a memoir prepared in book form by his medical colleagues and presented to his family as a mark of homage to his memory (54). This remarkable document contains not only the narrative of the doctor's life but also the clinical history of his last illness and the post-mortem findings. He had been honored at a public dinner on his 100th birthday when it is said, "he partook of the hilarity of the occasion with an ardent zest, and when called upon for a toast, offered in

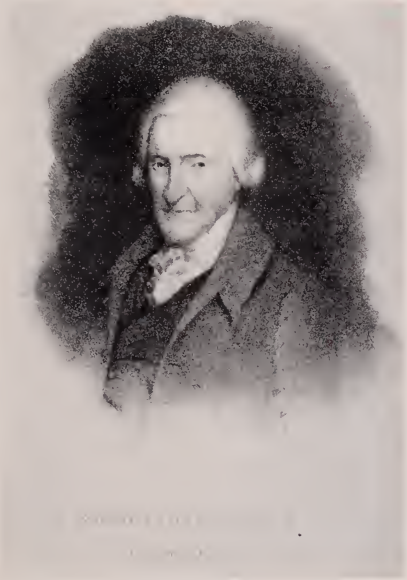


Fig. 5. Edward A. Holyoke, M.D. of Salem, Massachusetts

his own handwriting, a sentiment perfectly appropriate and professional, accompanied with a paternal and touching benediction upon the medical brethren present". At his death less than a year later, the autopsy revealed the obvious cause of death as gangrene of the left leg to the knee, and in addition an asymptomatic and unsuspected carcinoma of the stomach. Pierson reported this case in his paper because of the small circulation of the memoir.

Another venerable physician of colonial days, John Redman (1722–1808) of Philadelphia has been recently discussed by McDaniel in a study of his speeches and letters (55). The old gentleman, who was the first president of the College

of Physicians, constantly referred to his age and infirmity, always signing himself as, "your aged friend and fellow-servant."

No other contributions by Americans appear until 1837 when a report, signed only with the initials "J. M. W." is found in the Boston Medical and Surgical Journal, relating to post-mortem examination of a lady over 100 years old. Death had been accelerated by a fall resulting in a fracture of the hip. No obvious cause of death is apparent from the pathological findings. The author stresses the lack of ossification of the ribs, the absence of abnormal brittleness in the bones, the small size of the stomach and the presence of a large unsuspected fecal impaction (56).

In 1847 Caspar Wistar Pennock (1799–1867), Gerhard's colleague at Blockley, reported on the frequency of the pulse and respiration in the aged (57), pointing out that at one time the frequency of the heart's action was thought diminished with age until this was disproven by studies made at the Salpêtrière. His own observations on 170 men and 203 women led him to conclude that the frequency of the pulse of the aged is much greater than usually thought, while respiration is that generally admitted in reference to adults in middle life. This is the first quantitative clinical study of old age in American medical literature.

Jarrot (58) in 1849 described the amputation of the gangrenous leg of a Negro slave, aged 102 years. The patient stood the operation well but developed pleurisy on the fifteenth day and ceased. We are told that ether was ineffectual, that chloroform caused the patient to act as though intoxicated, and that brandy and laudanum were given to quiet him ante-operatively. Difficulty in management of the stump was experienced due to pressure of the adhesive plaster, and the use of sutures is advised.

In evaluating the knowledge of old age of the American physician in the first fifty years of the 19th century we must bear in mind that all of the outstanding men had studied in England and France. Pennock we know worked at the Salpêtrière, and Pierson learned the use of the stethoscope in Paris in 1832 (59). Likewise all the English medical texts were either imported or reprinted in the United States. The books of Carlisle and Day appeared in American editions, as did several of the encyclopedias of medicine. The paucity of contributions is perhaps best explained by the fact that medical literature in this country, in general, was very scanty until a much later date.

(To be Continued)

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CUTANEOUS MANIFESTATIONS OF SYSTEMIC DISEASE. II*

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BEAU'S LINES

These transverse furrows of all the fingernails are caused by sudden arrest of the function of the matrix usually in association with many different systemic diseases. Since the nails grow approximately one millimeter a week and since it takes the nail approximately one month to be seen beyond the proximal nail fold, the duration and time of the damage can be told with some accuracy. The systemic diseases include typhus, typhoid fever, the exanthemas and malaria. Arsenic poisoning and hepatic disease may also give rise to Beau's lines.

BEHCET'S SYNDROME

In this disease there appear simultaneous or separate episodes of aphthous (herpetic) lesions in the mouth and on the genitalia, and ocular changes. The involvement of the eyes usually assumes the form of a chronic, recurrent iritis, sometimes accompanied by uveitis and neuritis. The oral lesions are discrete, painful ulcers. The genital lesions are herpes-like vesicles, papules and ulcerations. Additional symptoms may include erythema nodosum, acneform eruptions and cerebral symptoms. The syndrome is more frequently encountered in men and is probably of virus origin.

BLASTOMYCOSIS

Blastomycosis is a term sometimes applied to a group of allied granulomatous conditions. In North America, it refers to the disease produced by the Blastomyces dermatitidis as distinguished from the paracoccidiodal granuloma of South America. The disease is most prevalent among farmers and frequently begins as a cutaneous pustule on the hands, face or ears. After several weeks, these lesions spread to form a patch of elevated, warty papules with a wide, sloping margin studded with miliary yellow abscesses (fig. 1). This is the characteristic lesion and the typical budding cells may be demonstrated in the tissue or cultivated on blood agar. These granulomatous, purulent lesions are followed by scarring. A small percentage of the cases show systemic involvement especially multiple abscesses of the lung and also of the bones, meninges and liver.

BOECK'S SYNDROME

(Besnier-Boeck-Schaumann's Disease)

This syndrome is described under the heading of sarcoidosis.

*This is the second and last installment of a Synoptic Atlas of Cutaneous Manifestations of Systemic Disease. The authors plan to publish the entire series in a single volume at an early date.—Ed.

BOURNEVILLE-PRINGLE SYNDROME

The manifestations of tuberous sclerosis in association with adenoma sebaceum, subungual warty fibromas and some phases of neurofibromatosis are grouped together under the heading of the Bourneville-Pringle syndrome. The skin lesions (adenoma sebaceum) consist of small, yellowish, pink, papules symmetrically distributed across the cheeks, nose and forehead (fig. 2). The symptoms of tuberous sclerosis depend primarily on the sites of involvement of brain tissue.

FIG. 1. Blastomycosis. Typical granulomatous lesion with margin studded with miliary abscesses. (Courtesy of Dr. Howard Fox.)

BROMIDE POISONING

The ingestion of bromides sometimes leads to a toxic state manifested by headache, vomiting, muscular weakness, somnolence or maniacal excitement. The establishment of a proper diagnosis may be assisted by the presence on the skin of one of two characteristic types of bromoderma. The more common variety is the acneform which resembles the lesions, and involves the sites, of acne vulgaris. Unlike acne, no comedones are present and the eruption is then composed only of papules and papulo-pustules. The less common variety of bromoderma is the granulomatous or vegetative, fungating type. The lesions of

the latter are usually encountered on the legs as elevated, granulomatous plaques or tumors (fig. 3).

BRUCELLOSIS

Cutaneous eruptions may be due to the consumption of infected milk or follow contiguity to infected animals. A typhoid-like roseola is seen in a small percentage of cases of undulant fever. Infection with B. abortus may be associated with four types of skin eruptions: (a) Arms directly exposed to the infection (veterinarians, farmers) may develop an itchy, red, follicular eruption which may become vesicular and then pustular; (b) a minute papular exanthem

FIG. 2. Adenoma sebaceum. The pinkish yellow papules are characteristically distributed across the cheeks, chin and forehead. (Courtesy of Dr. Frank C. Combes.)

on the chin, axillae and dorsum of the feet; (c) a bullous-hemorrhagic dermatitis resembling erythema multiforme; (d) pustules, vesicles and papules, at first at the site of exposure, but within fourteen days covering almost the entire body and associated with general adenopathy.

BRUSHFIELD-WYATT SYNDROME

The association of large angiomas of the skin with similar lesions involving the central nervous system is not uncommon. This syndrome is confined to cases of unilateral trigeminal port wine nevus associated with calcifying angioma in the opposite cerebral hemisphere.

BUBONIC PLAGUE

The infection produced by P. pestis is characterized by highly toxic phenomena and the development of either an intense adenitis (bubonic form) or a very

severe pneumonia (pneumonic form). The bubonic plague is often preceded by a primary lesion in the form of an itchy maculo-papule resembling a flea bite (rat flea). This lesion may represent the site of inoculation and usually persists throughout the disease, occasionally being transformed into a vesicle and finally into a carbuncle-like process. The adenitis (buboes) is usually limited to one walnut-sized, painful, doughy swelling but may be multiple. The inguinal glands are most frequently involved (50 per cent) and the axillary glands less so (25 per cent). Hemorrhagic infiltration of the skin is not uncommon and

Fig. 3. Bromoderma. Fungating, granulomatous lesions of the leg. (Courtesy of Dr. Frank C. Combes.)

manifests itself as a generalized petechial or ecchymotic eruption (black plague) with a predilection for the neck, breasts and extremities. In some cases, carbuncles subsequently appear on the skin as inflammatory or vesicular, necrotic patches; the necrosis may extend down to the bone and involve an entire extremity (cutaneous plague).

CALCINOSIS

Calcinosis cutis may be defined as a pathologic state in which calcium deposits are laid down in the skin and subcutaneous tissues. It may be divided into two main groups:

The first group, calcinosis universalis (Profichet's syndrome), includes those cases due to a disturbance of general calcium metabolism such as hyperparathyroidism. Clinically, these patients present sharply circumscribed, variously sized plaques and tumors and erythematous macules in the vicinity of large joints. The lesions may ulcerate and extrude calcific masses. If associated with hyperparathyroidism, there is also decalcification and tumor-like swellings of the bones, hypotonic musculature, increased blood phosphatase and hypercalcemia. Calcinosis universalis also occurs in scleroderma, dermatomyositis,

Fig. 4. Calcinosis cutis. Firm calcareous plaques in association with swelling of the fingers. (Courtesy of Dr. Howard Fox.)

poikiloderma, myositis fibrosa and acrodermatitis chronica atrophicans. Metastatic calcification in the skin is rare. The Thibierge-Weissenbach syndrome groups calcinosis, scleroderma and pigmentary abnormalities.

The second group, or localized variety, is entitled calcinosis circumscripta and is a result of local tissue dystrophy. The hands and elbows are most frequently involved. The lesions are firm, calcareous plaques in association with swelling of the fingers (fig. 4). Associated diseases include acrosclerosis and Raynaud's syndrome. Calcification also occurs in various benign and malignant epithelial tumors (sebaceous cysts, dermoid cysts, xanthomas and sarcomas),

chronic inflammatory lesions, arteriosclerotic patches, caseous tuberculous nodules, cysts due to parasites such as Trichinella and scars.

CAROTENEMIA AND CAROTENODERMA

Canary yellow or lemon coloration of the skin, especially of the palms, soles and face, may be due to the ingestion of an excess of carrots and other sources of carotene. It should not be confused with jaundice (bronze, orange, deep yellow)

FIG. 5. Cavernous sinus thrombosis. (Courtesy of Dr. Franklin H. Tops and the Clay-Adams Company.)

and unlike the latter, it does not produce yellowing of the sclera or pruritus. This whiteness of the sclera is the chief clinical differential sign.

CAVERNOUS SINUS THROMBOSIS

Thrombosis of the cavernous sinus causes dilated facial veins, protrusion of one or both eyeballs and sometimes papilledema with pain above the corresponding eye and immobility of the eyeball. The skin assumes a dusky red color over the entire region with the veins standing out in bas-relief (fig. 5). Signs of a furuncular infection (which may have produced the thrombosis may still be evident on the skin.

CELIAC DISEASE

Pellagra-like eruptions and pigmentation of the skin are not uncommon in this disease due to an actual deficiency of nicotinic acid (lack of absorption from intestinal tract). Other avitaminoses may also be present.

CHOLERA

The dehydration and diarrhea of cholera are accompanied by dryness, inelasticity and wrinkling of the skin. In the later stages of the disease, especially with renal involvement, fleeting erythematous and urticarial eruptions may be observed.

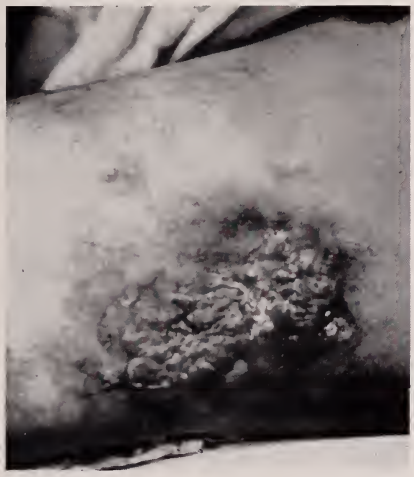

FIG. 6. Coccidioidal granuloma. (Courtesy of Dr. Frank C. Combes)

CIRRHOSIS OF THE LIVER

Distended venules and telangiectases are commonly seen on the face and nose, both of which may be flushed. Rosacea and even rhinophyma may be present. Spider nevi and pulsating angiomas appear in groups on the back, neck, shoulders or arms. A visible engorgement of the veins in the epigastric region of the abdomen is of importance because it occurs earlier in cirrhosis than in other intra-abdominal diseases, and is usually above the umbilicus rather than below as in the others. Jaundice may mask the usual pallor of the late cirrhotic. Subcutaneous ecchymoses are a late sign. Palmar erythema (liver palms) may be present but is not characteristic.

COCCIDIOIDOMYCOSIS

The California disease has attained more prominence and dissemination since its contraction by troops stationed in endemic desert areas. Subsequent to the inhalation of the spores of Coccidiodes immitis, the patient develops symptoms of a sever upper respiratory infection followed by erythema nodosum (5 per cent of cases). The majority of these patients recover, but in a small percentage, the acute non-fatal type is followed by the highly fatal progressive form, coccidioidal granuloma. This form affects the lungs most frequently with symptoms resembling those of diffuse miliary tuberculosis. The skin, lymph nodes, bones, meninges and other tissues may also be affected. The cutaneous lesions are elevated, soft granulomas which ulcerate and discharge a thick, ropy, yellow-gray pus (fig. 6). The organism may easily be demonstrated in the pus or

Fig. 7. Necrotizing ulcer of the leg in a patient with ulcerative colitis. (Courtesy of Dr. Joseph Felsen and the Clay-Adams Company.)

cultured from it on Saboraud's medium. The granulomas may eventuate in flaccid, deep abscesses or in nodular, papillomatous elevations resembling blastomycosis or tuberculosis verrucosa cutis. Skin tests with the fungus extract (coccidioidin) are specific and indicate past or present infection.

COLITIS

The chronic ulcerative form of colitis gives rise to various avitaminoses and deficiency states. The skin is dry and scaly with follicular hyperkeratosis, pigmentation and erythematous eruptions. The tongue may show atrophy and inflammation of the lingual papillae. Reports have been published of necrotic cutaneous ulcers which were present on the skin only during an exacerbation of this disease. The progress in healing of these ulcers kept pace with the status of the intestinal disease (figs. 7, 8 and 9). Erythema nodosum is not uncommonly seen according to Crohn in the early phase of chronic ulcerative colitis. Aphthous stomatitis and condyloma acuminata may also be associated with this disease.

FIG. 8. Superficial ulceration of the foot in a patient with ulcerative colitis. (Courtesy of Dr. Burrill B. Crohn.)

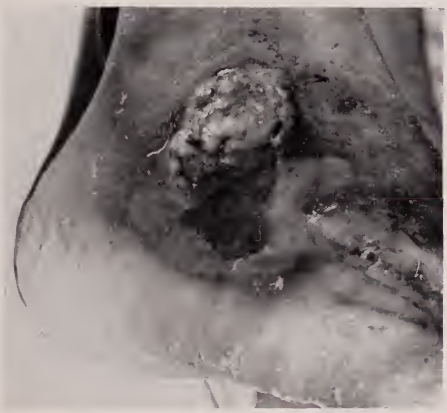

FIG. 9. Deep ulceration of the foot in a patient with ulcerative colitis. The progress in healing of this lesion kept pace with the status of the intestinal disease. (Courtesy of Dr. Burrill B. Crohn.)

CORONARY OCCLUSION

The skin has an ashen-gray pallor and is cold and clammy during the attack. The more than average association of xanthelasma and psoriasis with victims

of this disease is of unknown significance although the former is probably related to an underlying atherosclerosis.

CULLEN'S SIGN

This sign consists of hemorrhage into the skin resembling the changes following a bruise. The color varies from blue green to yellow, and the location is in the vicinity of the umbilicus. It signifies intraperitoneal hemorrhage, not infrequently due to a ruptured ectopic pregnancy.

CUSHING'S SYNDROME

Basophilic adenomas of the pituitary gland are characterized by painful adiposity of the face and neck, kyphosis, sexual dystrophy (amenorrhea, impotence), hypertension, abdominal and lumbar pains and weakness. The cutaneous changes are usually a dusky or plethoric appearance of the skin (face especially) with abdominal striae distensae (purple, red or brown). The skin may be quite dry and scaly. Less commonly, the skin manifestations include acrocyanosis, cutis marmorata of the extremities, purpura and xeroderma. The purpura and ecchymoses represent a tendency toward hemorrhage and bruising without apparent cause. The anterior aspect of the legs is especially affected, and acrocyanosis may be present. The skin over this area is usually thin and shiny, and may show a diffuse brownish or bronze pigmentation from the ankle to the knee.

Early in the disease, there is a thinning of the hair on the head and the appearance of body and facial hirsutes. The hair on the head recedes especially over the vertex and in the temporo-frontal regions as in the male. At the same time, the hair grows on the upper lips and beard, over the thighs and legs, forearms, chest and abdomen. The pubic hairs form an inverted triangle towards the umbilicus. The hypertrichosis is not always as excessive as that due to adrenal tumors, and may approximate that of the male more in its characteristic distribution than in its intensity. Brownish pigmentation of the skin may be limited to the face, axilla and nipples. In those cases presenting enlargement of the clitoris, extreme hirsutes and greasy, acneform skin, the syndrome may be produced by a neoplasm of the adrenal cortex.

DENGUE FEVER

This tropical disease is characterized by an abrupt onset, pains in the joints, muscles and head, fever and a non-specific, erythematous eruption of the face and trunk. After a stage of remission, the fever and pains return and are associated with a polymorphous eruption in from 10 to 100 per cent of the cases. This eruption may be maculo-papular, scarlatiniform, urticarial or rarely, petechial. The lesions appear first on the palms and backs of the hands and extend up the arms to involve the entire body. Branny desquamation follows the eruption and disappears in several weeks.

DERMATOMYOSITIS

This disease of unknown origin is usually characterized by inflammation and sensitivity of various groups of muscles and the underlying cutaneous tissue in association with a non-specific cutaneous eruption. The systemic findings

also include fever, hyperhidrosis, dysphagia (muscular weakness), creatinuria and enlargement of the spleen. The cutaneous eruption may resemble lupus erythematosus, urticaria, erythema nodosum or eczema and usually appears over the affected muscles. In many of the cases, there occurs a diffuse hardening of the skin due to an underlying solid edema usually limited to the face and extremities. Erythema, if associated, is rosy or livid and diffuse or mottled. Mild pigmentary and atrophic changes sometimes accompany the erythema.

In recent years, much discussion has evolved around the association of this disease with diffuse malignant scleroderma (perhaps the same disease) and acute disseminated lupus erythematosus. A certain percentage of the cases show features common to two of these disease, or occasionally, to all three. In both dermatomyositis and acute disseminated lupus erythematosus, there may occur joint pains, fever, photosensitivity, leukopenia, splenomegaly, Raynaud-like symptoms, lymphadenopathy, alopecia of the scalp, sterile blood cultures, muscular involvement, renal disease (albuminosis and microscopic hematuria), and similar cutaneous lesions. The differential diagnosis may be extremely difficult and several helpful points have been enumerated by Keil. At times, both diseases may run an afebrile course and the clinical picture may be dominated by the sequelae of these conditions. The average typical example of each, however, has a fairly distinctive course. Acute disseminated lupus erythematosus shows a predilection for young women, while dermatomyositis is more likely to occur in males, and in older persons. However, there are numerous instances of both conditions in all age groups and both sexes. With reference to the cutaneous lesions, the following points tend to favor the diagnosis of dermatomyositis: (1) early or initial involvement of the eyelids by a peculiar type of erythematous and telengiectatic edema; (2) special atrophic areas (soft and hard) over the small articulations of the fingers, occasionally the larger joints and trunk; (3) large areas of noncircumscribed erythema in relation to large masses of simultaneously affected muscles and subcutaneous tissue; (4) occasional occurrence of an unusual degree of hypertrichosis, generally on sites of previously inflamed adjacent structures; (5) peculiar whitish areas in the oral mucosa, tongue, etc.; (6) periungual and other changes. In both acute disseminated lupus erythematosus and dermatomyositis the cutaneous lesions may be absent or occur late in the course. When this is the case in disseminated lupus erythematosus, the following criteria have been set up for facilitating the diagnosis; (1) cases of "rheumatoid arthritis" in which there is sensitivity to sunlight, with subsequent or simultaneous involvement of the kidneys, serous membranes and other parts; (2) cases of febrile thrombopenic purpura in which cultures of the blood are sterile and there is involvement of such organs as the kidneys; (3) peculiar examples of polyserositis with widespread involvement of other systems, including the renal tissue. Small muscles of the hands may be involved in both conditions, but more commonly in dermatomyositis in which is also seen involvement of the pharyngeal, intercostal, diaphragmatic and ocular muscles. The subcutaneous tissues are often implicated in dermatomyositis but rarely in acute disseminated lupus erythematosus. Articular involvement is frequent in disseminated lupus erythematosus, but rare in dermatomyositis, at least in a

pathologic sense. However, one encounters articular deformities due to contracture produced by fibrosis. Disseminated lupus erythematosus affects the kidneys in a high per cent of cases. As a rule the kidneys are spared in dermatomyositis. Ophthalmoscopic examination often shows alterations of the fundus in disseminated lupus erythematosus but cases of dermatomyositis generally reveal no abnormalities. Endocardial disease is grossly evident in 30 to 50 per cent of cases of disseminated lupus erythematosus but the endocardium seems to be spared in dermatomyositis. The reverse is true for myocardial involvement. Involvement of the serous membranes is a feature of great importance in disseminated lupus erythematosus and is generally primary and independent. This is rare in dermatomyositis. Involvement of the lymph nodes is less common in the latter. The prognosis is grave in disseminated lupus erythematosus; it is less grave, but still serious for dermatomyositis.

DIABETES MELLITUS

The skin manifestations of diabetes are many and of protean nature.

1. Pruritus. Itching is probably the most common cutaneous symptom of diabetes and is present in 25 per cent or more of the cases. The anal and genital regions are the most usual sites, and pruritus vulvae should always be an indication for the performance of urine and blood glucose determinations. Generalized pruritus is uncommon.

2. Furuncles and carbuncles. Single or recurrent episodes of these lesions should always necessitate the elimination of diabetes as an etiologic agent. Infections of the hands and feet are also common in diabetics following slight trauma and the grim spectre of gangrene is omnipresent.

3. Fungus infections. Dermatophytosis of the feet is the most common cutaneous disease encountered in diabetics; the incidence is much greater than in normal individuals. Moniliasis, due to M. albicans, is a frequent forerunner or accompaniment of diabetes. The localized manifestations produced by this yeast include paronychia of one or several fingers; thickening and ridging of the nails without loss of luster; typical, bright red, scaly and exudative intertrigo of the axillae, groin, toe webs, umbilicus and inframammary folds (fig. 10); perleche (intertrigo of the corners of the mouth); erosio interdigitalis blastomycetica (intertrigo of the third and fourth finger webs) and vaginitis. The generalized cutaneous and systemic forms of moniliasis are rare but are mentioned because all patients with moniliasis are candidates for diabetic case finding.

4. Xanthoma eruptivum. This disease is usually referred to as xanthoma diabeticorum, a misnomer as observed in a previous publication. The disorder is not due to the diabetes per se but is rather a reflection of the pathological hyperlipemia frequently encountered in diabetes mellitus. The eruption may, however, also be encountered during the course of hyperlipemias from any cause (biliary disease) and thus the term diabeticorum is a misleading one. The lesions are small, yellow papules with a surrounding, inflammatory areola. They closely resemble pustules in appearance but are solid and extrude no pus on incision. The papules are commonly grouped around the buttocks, elbows and knees (fig. 11).

5. Necrobiosis lipoidica diabeticorum. This disease primarily affects the

FIG. 10. Monilial intertrigo. The lesions are bright red in color. The satellite vesicopustules are characteristic. (Courtesy of Dr. Royal Montgomery.)

FIG. 11. Xanthoma eruptivum. (Courtesy of Dr. Frank C. Combes)

lower extremities of women, 90 per cent of whom are diabetic. The lesions commence as hard, red papules which enlarge at the periphery and gradually become depressed in the center to form a plaque-like ring. After a period of time, the center assumes a waxy, yellowish color latticed by thin telangiectases and shading into violet at the margins. The skin over the central depression finally becomes tense and atrophic and has been likened in appearance to a "tight layer of cellophane." Histologically, the process resembles that of a localized diabetic gangrene.

6. Insulin reactions. Tender areas may develop following the first few injections of insulin. In a small number of cases, depressed atrophic areas of lipodystrophy may appear in the region of the insulin injection.

7. Avitaminoses are frequently encountered in diabetics. Of these, pellagrous changes are most common.

DIABETES INSIPIDUS

In this disease, the skin and mucous membrane are very dry.

DIPHTHERIA

The systemic disease is sometimes associated with an evanescent erythema of the trunk and extremities. Actual diphtheria of the skin is most often seen as superficial grayish ulcers surrounding an inflamed erythematous abrasion or superficial infection.

ABSTRACTS

Authors' Abstracts of Papers Published Elsewhere by Members of the Mount Sinai Hospital Staff

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

Psychoanalytic Investigation of Reaction to the War Crisis of Candidates for Induction. S. Lorand. Psychoanalyt. Rev., 32: 1, January, 1945.

On the basis of an analysis of a patient with diffuse anxieties, this study emphasizes the importance of the pre-traumatic personality in the war neurosis. The relationship between general neurotic anxiety and the special type of neurotic reaction exhibited by soldiers exposed to danger is discussed, while at the same time the author points out the basic differences between these two types of anxiety. He states that whereas in the general neurotic anxiety the fear arises as a defense against unconscious strivings (as for instance in phobias), the anxieties and symptoms exhibited in the traumatic war neuroses can be traced to the ego. When one is in actual danger the whole ego is threatened and the drive for self-protection usually manifests itself in "flight in illness." The patient whose analysis is presented, clearly showed a personality which was predisposed to traumatic reactions and at the onset of the war emergency regressed toward a narcissistic state. His neurotic reaction closely resembled the type exhibited in war neurosis. In the predisposition to traumatic reaction, both constitutional and emotional factors are involved. His anxiety reactions and regressive tendencies were due to the hostile tension which had been accumulating for many years. As a result of early forceful discipline all outward expression of aggression had been repressed, but the war mobilized and reactivated the once forbidden, cruel impulses. At the same time, the threat of Army discipline revived his childhood memories and he could not bear the thought of again being disciplined. Feeling threatened by all these conflicts he tried to withdraw in illness.

Acute Suppurative Bronchopneumonia. H. Neuhof and A. Thomas. Arch. Int. Med. 75: 45, January, 1945.

Suppurative bronchopenumonia, a descriptive term for an acute infection of the lung which has been long known under various names, is not rare and yet it is the subject of only a fragmentary literature. A systematic presentation of the subject has been attempted on the basis of a study of 120 well documented cases. Since the disease presents the features of an infection of the upper respiratory tract descending into bronchopulmonary segments, the pathogenesis of suppurative bronchopneumonia appears to be identical with that of nonsuppurative aspiration bronchopneumonia. The pathologic features consist of a severe bronchopneumonia involving one, several or many portions of the lung or lungs. Substantial portions of bronchopulmonary segments are involved. Spread from primary areas appears to be chiefly by the mechanism of spillover. Varying degrees of suppuration and necrosis occur within the affected segments of lung, usually with the formation of single or multiple foci of liquefaction with areas of bronchopneumonia. Necrosis is at times outstanding and spectacular. The term "necrosuppurative bronchopneumonia" appears appropriate under such circumstances. The microscopic feature of suppurative bronchopneumonia is a combination of suppuration and necrosis in varying degree. In addition there is seen at times a nonspecific arteritis with thrombosis. The roentgen features are extremely varied and often bizarre. The six main types which are set forth may exist singly

or in various combinations. One or more areas of rarefaction in the midst of pneumonic infiltration comprise the characteristic feature. The essential symptoms are initial thoracic pain which is at times severe, cough, expectoration of substantial quantities of purulent sputum (in adults) and fever. The physical signs are not distinctive. Suppurative bronchopneumonia, including the necrosuppurative variety, is a self-limited disease which is not materially influenced by any of the currently employed sulfonamide compounds or by serum therapy (in the group of cases due to pneumonococci). The treatment is primarily supportive and when vigorously pursued may greatly facilitate recovery.

Allergic Dermatitis Due to Metallic Cobalt. S. Peck, L. Schwartz, K. E. Blair and K. E. Markuson. J. Allergy, 16: 51, January, 1945.

Dermatitis occurring among employees in a plant that manufactures cemented carbides was investigated. Sensitivity to cobalt was found to be the cause of the dermatitis. Recommendations for prevention are given.

Influence of Depletion of Diffusible Electrolytes Upon Electrical Activity of the Brain. E. P. Pick and M. M. Miller. J. Neurophysiol., 8: 47, January, 1945.

Frogs can be depleted of 30–40 per cent of their body chlorides by being immersed in distilled water for periods of several days or weeks. This depletion of NaCl associated with the loss of other diffusable substances as, for example, potassium and calcium salts as well as glucose reduces the electrical brain activity, which is characterized in part by the appearance of Delta-like waves (Type A) and further in a marked reduction in wave frequency and amplitude (Type B). Both of these alteration types can appear at intervals alternately. The degree of reduction of electrical activity can vary in different brain areas and the depresed activity can be restored by intralymphatic injection of small amounts of NaCl. When the electrical activity has been too severely impaired by the excessive loss of diffusible substances, it is not possible to restore the activity by means of administering either NaCl, KCl, or Vitamin B_1. The successful treatment of shock with saline may be in part explained on the basis of the central action of saline in improving the electrical activity and thereby aiding the restoration of the impaired vital centers. The depression of the electrical brain activity is explained as due to the inhibitory effects upon the oxidative processes of the brain resulting from the loss of NaCl and glucose.

The Effect of Curare and Curare-like Substances on the Central Nervous System. E. P. Pick and K. Unna. J. Pharmacol. & Exper. Therap., 83: 59, January, 1945.

Crystalline d-tubocurarine, dihydro-beta-erythroidine, quinine ethochloride, nicotine and thiamine inhibited and suppressed the electrical activity of the frog brain. Prostigmine, which itself depresses brain potentials, failed to influence the effect of these substances on the brain potentials, although it counteracted their effects on the neuromuscular junction. Prostigmine partially inhibited the electrical activity of the frog brain; a subsequent injection of acetylcholine suppressed the electrical activity completely. Monoidoacetic acid and sodium cyanide abolished the brain potentials of pithed frogs. The findings are interpreted as an inhibition of central synaptic transmission by curare and substances with a curare-like action.

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THE EDWARD GAMALIEL JANEWAY LECTURE

THE SWORD AND THE PLOUGHSHARE*

CORNELIUS P. RHOADS, M.D.

Director of the Memorial Hospital for the Treatment of Cancer and Allied Diseases and the Sloan-Kettering Institute for Cancer Research, New York, New York

Whereas the title of this Janeway lecture could be understood as indicating a review of a variety of medical developments made through wartime research, the presentation is actually limited to a single topic. This includes a number of different aspects of a coordinated study of one group of military toxic chemicals, the mustard gas analogues. I have thought it wiser to present more or less completely one subject rather than to treat superficially a greater number. This course was chosen in order to prove that military research, pragmatic to the highest degree, can be so conducted as to yield results of great value for the peace.

The Bari Diaster. For a moment I would like you to relive the dark military days of the winter months of 1943. At that time our troops were retaining a somewhat tenuous foothold on the southern third of the Italian peninsula. The harbor of Bari was a principal military port of supply. On the night of December 3, the cargo ships, discharging urgently needed supplies and munitions, were closely packed. In some manner as yet undisclosed the air-raid warning and protection service failed, and at 7:30 o'clock enemy bombers were overhead. The raid was brief and only four ships were hit, all with high explosive bombs. These four were enough. The vast cargoes of fuel and explosives flared up into a sea of flame and a volley of tremendous detonations. Sixteen ships blew up and sank. Four more were seriously damaged.

Almost exactly in the center of the moored vessels, next to the mole, was the Liberty ship, John E. Harvey, loaded with 100 tons of mustard gas in airplane bombs, among several thousand tons of high explosive munitions. The Harvey, though unhit by the enemy bombs, lifted suddenly in a gigantic blast and disappeared. No living person of her complement was ever seen again.

The entire harbor area was an indescribable mass of smoke, flame, sinking ships and exploding munitions. The water was covered with a thick layer of burning oil in which a thousand men died. The uninjured, despite disrupted organization and communication, worked frantically to salvage survivors and precious equipment, vaguely aware that this was no ordinary raid damage, aware that some unusual element was present. Later checks revealed that many men commented on the curious garlic-like odor to the smoke. Some cool heads, even in the uproar and confusion, had the wit to refer the smell to an excessive intake of garlic by the local Italian population. The crew of one

*Read at the Blumenthal Auditorium, October 2, 1946.

destroyer, careening through the inferno, found that their eyes were so badly inflamed that they could scarcely see to dock their vessel and could not take it out again. On another ship, widely separated from the group, some unidentified person ordered a gas alarm. Masks were broken out and worn for a few minutes only, when the order was countermanded and an all-clear sounded. As far as is known, this was the only recognition of the presence of poison gas in the air.

The hastily formed rescue squads pulled something over 1,000 men from the oil-covered, blazing, bitter cold water. These casualties were routinely wrapped in blankets, and without removal of the oil, were laid out in rows on stretchers on the ground of hastily improvised dressing stations. It was noticed that a small number of these men were curiously apathetic and weak almost to the point of paralysis, a fact at first ascribed to unusually severe immersion shock. This view was supported, it was thought, by the demonstrable profound hemoconcentration and hypotonia. The fact was commented on, however, that these men showed less restlessness, anxiety and tachycardia than shocked casualties would be expected to present.

By the second day the situation was clear. The few men who had independently removed the oil from their bodies were well; the remainder, still black with the fuel, were obviously dying. The outstanding manifestations were a terribly severe conjunctivitis and a generalized, brawny edema of the skin and subcutaneous tissue. As the days went on, the syndrome became a very characteristic one. The original hypotonia, which had failed completely to respond to therapeutic measures which are ordinarily effective, disappeared, as did the hemoconcentration. The leukocyte count, originally moderately elevated, changed to show a disappearance, first of lymphocytes, and later of polymorphonuclear forms. Total counts reached levels as low as 50 to 100 cells per cmm. in some instances. All the men with evidence of profound depression of leukocyte formation died, but did not evince the disorders, such as stomatitis, so uniformly associated with agranulocytosis of the type seen after benzol or pyramidon.

There was at this time in North Africa, at the area headquarters, a medical officer trained in the Chemical Warfare Service, Col. John A. Alexander, of a distinguished medical family. He heard of the bombing shortly after it occurred, and learned that some casualties had complained of conjunctivitis. This officer realized the true situation: that the casualties were not shocked from immersion or blast, but were dying from the late results of mustard gas poisoning. Col. Alexander wrote a most detailed, indeed, a classic report. He did more, he saved tissue in hastily improvised fixative, and sent the specimens with a personal letter, to the Medical Laboratories of Chemical Warfare Service in this country. All of this was done in anticipation of the reports which would follow through the official channels perhaps six months later. The material was received and reviewed at Edgewood Arsenal within a few weeks of the disaster, and provided the first confirmation of a hazard of military medicine which had already been anticipated and prepared for.

The Research Done in Anticipation of Chemical Casualties. Before the actual

outbreak of World War II, Secret Service information made clear the fact that both the Germans and the Japanese not only intended to use poison gas, but were preparing to do so on a very large scale. Our army, its research hampered by financial limitations, had made few moves since World War I to anticipate the offensive or defensive problems of chemical warfare. Immediate scientific preparations were imperative and were undertaken.

The same pattern of research organization in chemical warfare was followed as was established for the solution of other scientific problems which perplexed the military and naval authorities. An administrative office for dispensing funds in support of and for the management of the needed investigative work was created by presidential directive under the title of Office of Scientific Research and Development. The medical part of this organization, the Committee on Medical Research, received recommendations submitted by one or the other group of the National Research Council. In the case of chemical warfare research, this was the Committee on Treatment of Gas Casualties, under the chairmanship of Dr. Milton C. Winternitz, Professor of Pathology at Yale University Medical School. He is known for his energy and distinguished for his contributions to the pathology of injuries due to toxic agents during World War I. In parallel with the civilian organization, there was created by the army a medical group under the Surgeon General, assigned for function and for administration and discipline to the Chemical Warfare Service, and known as the Medical Division of that branch. This organization, committed to research on both offensive and defensive aspects of military toxic agents, hastily built its own laboratories and field stations. During the development of its organization and personnel, the Medical Division gradually took over the OSRD function of financing and directing the research work on chemical warfare in civilian laboratories until, by the spring of 1945, it had essentially completed the shift. It then operated the laboratories under an advisory committee composed of the former chiefs of the civilian groups, but financed and directed by the army. Under the civilian OSRD, contracts were assigned to already existing research laboratories in universities and industrial concerns. The policy under which these contracts were allotted was a collaborative one with the Army designed to meet the immediate military need and coincidentally to allow the assumption of the contracting function by the Army as fast as the military laboratories and organization were qualified to do so.

From the first, it was apparent that of all the poisonous chemicals which had been studied, the compounds allied to the mustard gas used in World War I possessed from all points of view the greatest military potentiality. The factors of ease of procurement, practicability of dispersion by any type of munition, including the airplane bomb, the high toxic value and the general nature of the intoxication with the attendant difficulty in developing defensive measures, all made mustard and its analogues the poisons of choice. Furthermore, the enemy gave evidence of having in large scale procurement one or the other of a group of modified mustard compounds known as the French, or nitrogen mustards. A close chemical relationship exists between these substances and the classic sulphur

mustard of the first World War. The various considerations hitherto specified made imperative a detailed study, not only of the offensive value of the newer mustard analogues, but also of the mechanism by which they exert their poisonous effects. Only through a knowledge of this mechanism could adequate measures for protecting our troops be instituted, as well as procedures for treating adequately those men who became gas casualties in spite of defensive equipment. Accordingly, the problem was split into its constituent parts and research on each part was assigned to the particular university laboratories most qualified to conduct it successfully.

The problem broke naturally into three divisions, as follows: a) the chemical changes undergone by the nitrogen mustards in the course of their metabolism in the body; b) the effects upon essential bodily constituents of each one of the metabolites of the poison; and c) the general pharmacological effects of the compounds. The results of the studies will be discussed under these three headings.

Chemical properties of the nitrogen mustards. These compounds are characterized by their ability to change in water solution. The poisonous properties appear to be possessed by certain of the products formed during the change, which takes place quite rapidly. The alteration is known as cyclicization. One chlorethyl radical forms transiently a single ring. If two radicals are present, as in the case of the typical nitrogen mustard, HN_2, two rings are formed, and in the case of the tris compound, HN_3, of course three rings would be encountered. The speed of the formation of these rings, their reactivity and the rapidity of their subsequent conversion to less active radicals, was a particularly important feature of the chemical study. It was learned that for each of the mustard analogues the speed of ring formation and ring breakdown varied. It was also learned that the ring was the reactive form which caused damage by combination with essential chemical constituents of body tissues.

The reactivity of the ring, known as the imine form, is well illustrated by the reaction between the cyclicized HN_2 and the amino acid alanine. The imine, or imonium, form has been shown to alkylate the functional groups, and so render biologically unavailable the following compounds: The α-amino, imidazole, sulphydryl, sulfide, phenolic, ϵ-amino, and imino groups of amino acids and peptides; inorganic phosphate as well as glycerophosphate and hexose phosphates; the amino groups of adenosine and thiamine; and the pyridino-N of nicotinic acid amide and pyridoxine. The fact must be recalled that these reactions have all been shown to take place with pure compounds in the test tube. Little evidence is available to prove that the same reactions occur in the living cell, although they may well do so.

Not only do the imine rings formed in the course of metabolism and hydrolysis of the nitrogen mustards react with pure tissue constituents; they also inhibit the catalytic activity of a number of important enzymes. It is curious that whereas certain enzymes are profoundly interfered with, others seem to be quite resistant. By and large, the concentrations of the toxic chemical required to inhibit these kinetically active systems are somewhat greater than the concentrations to which they would be exposed in the course of fatal poisoning of the

whole animal. It is, therefore, uncertain whether the inhibition of enzymes as demonstrated in the test tube, actually takes place *in vivo*. It is important that the enzymes affected, insofar as the studies have gone, appear to be certain ones, such as hexokinase, which are concerned with the provision of energy through phosphorylation, and choline esterase, which is important for the transmission of the nerve impulse at the myoneural junction. The clinical importance of this reaction will be discussed later.

Effects upon essential bodily constituents. Barron has studied the changes in the enzymatic activities of tissue of whole animals poisoned by the nitrogen mustards. He proved that there resulted a decrease in the ability of the liver to form urea and of the kidneys to metabolize pyruvate and choline.

Not only do nitrogen mustards react with pure constituents which can be isolated from tissues, but they also appear to have some h therto il'-defined, perhaps generally denaturing, action on proteins. They will, for example, combine quickly with the globin of hemoglobin. At one time when these substances were terribly feared because of their abilities to destroy the eye, it was proposed that if soldiers who were exposed, pricked their skin and obtained a drop of blood, they might apply it to the cornea as a protective film. Fortunately, this never became necessary. Denaturing interactions with a variety of proteins other than hemoglobin take place. These proteins include those of certain plant disease viruses, notably the virus of Tobacco mosaic. It is wholly possible that the denaturation reaction is one of the most important ones in explanation of the biological effects of these poisonous substances.

Pharmacological effects. The pharmacodynamic actions of the mustard compounds are similar, and are seven in number, as follows: (1) para-sympathomimetic, (2) nicotinic, (3) paralytic, (4) central, (5) vesicant, (6) nucleotoxic, and (7) leukopenic. These various effects are caused by the different chemical substances formed during the conversion in the body of the nitrogen mustards from their original form to the final or stable form. This was first proven by an ingenious experiment of Gilman, who allowed a solution of HN_2 to stand in water at room temperature. At various intervals samples of the material were withdrawn and injected into experimental animals. Since, under standard conditions, the conversion from the original substance to the end-product through the intermediate steps occurs at a predictable rate, it is possible in this way to inject samples containing predominantly one or the other compound formed in the various steps.

1. *Parasympathomimetic action.* These effects are marked by the conventional signs of vagus stimulation such as miosis, salivation, diarrhea and spasm of the pyloric sphincter. As would be expected, they can be abolished to some extent by atropine. They are cholinergic, and are explainable by two mechanisms. The first of these is the similarity to choline of the chlorimine formed in the hydrolysis of the nitrogen mustard. It is supposed, of course, that this structural similarity is associated with a functional likeness, so that the chlorimine is functionally active as choline. The second way in which cholinergic effects are exerted is by the power of the chlorimine to combine with and inactivate cholin-

esterase. By this inactivation of the natural choline inhibitor, an abnormally great amount of choline becomes available at the myoneural junction and muscle stimulation follows. It is believed that this enzyme inhibition is an important factor in poisoning due to these compounds, since the resistance to them shown by the fowl can be correlated with a high degree of resistance of its cholinesterase system.

2. *The nicotinic effect.* This is very striking under the proper experimental conditions and takes the form of a well-defined inhibition of the conduction of nerve impulse, shown by a flaccid paralysis.

3. *The paralytic effect.* This can be differentiated pharmacologically from the nicotinic effect just described. It appears to be due to a direct inhibitory action of the toxic compound on those phosphorylating enzyme systems, previously specified, which are necessary to provide the energy for muscular contraction.

Both the nicotinic and paralytic effects which can be defined so beautifully by the standard laboratory methods were undoubtedly operative in causing the profound apathy and weakness shown by the casualties at Bari.

4. *The central effect.* This is marked by nausea and vomiting when mild, and by convulsions and death when severe. Central stimulation appears to be the principal mechanism which causes fatality from poisoning by large doses. The nausea is regularly seen and may be a distinctly troublesome complication of the therapeutic use of the nitrogen mustards.

5. *The vesicant action.* The nitrogen mustards were developed as agents which had a profound local and systemic toxicity. They injure severely any tissue with which they come in contact, particularly epithelial tissue. This explains why the men at Bari had the brawny edema of the skin exposed to the dilute solution of mustard in the fuel oil. The ability of the mustards to cause local injury makes thrombosis a serious problem, especially if one of the compounds of rapid reactivity is allowed to seep outside of a vein in the course of a therapeutic intravenous injection.

6. *The nucleotoxic action.* The effects of the nitrogen mustards on nuclei are best studied in the epithelial cells of the cornea of the eye and the cells of lymphoid and hematopoietic tissue. These organs are composed of units which proliferate rapidly and hence are peculiarly susceptible to substances which affect adversely the nuclear components concerned with cell division.

The earliest observations on the action of the nitrogen mustards on nuclei were those of Friedenwald and his associates at the Johns Hopkins University. In the course of their studies on the mechanism of nitrogen mustard injury to the eye, they investigated the effects on mitosis of exceedingly low concentrations, too low, indeed, to cause gross evidence of injury of systemic intoxication. The result was surprising and dramatic. A prompt inhibition of mitotic activity resulted and endured for a number of hours. The findings were confirmed by observations on the mitotic activities of bone marrow and of other tissues. The British workers were quick to develop the study of nuclear effects and to convert it to other types of experimentation on material more suitable to the disclosure of details of the action. Auerbach and Robson, of Edinburgh, produced mutations

in the fruit fly, Drosophila, in a fashion very much like those observed after x-rays. As with x-rays, chromosome translocations, aberration and inversions were induced, with sex-linked, both lethal and non-lethal mutations. Well defined interference with the cleavage of Arbacia eggs, sea urchin eggs and Tradescantia seeds was demonstrated. A most interesting observation is that of Bawden and Pirie, working on the suggestion of Robson. These investigators studied the effect of HN_2 on the infectivity of the viruses of Tobacco mosaic and Bushy Stunt disease. They found that following the use of proper concentrations of HN_2, no detectable chemical change of the virus took place, but the infectivity was enormously reduced or lost altogether. The change was associated with a pronounced alteration of the ability of the virus to crystallize. Further information on the nature of this change will be awaited eagerly, since it might be of tremendous importance in understanding what physical or chemical property of a virus is responsible for its pathogenic power. It would also be of great importance to know whether HN_2 or its analogues also are effective in inactivating other viruses. The fact is suggested by the work of Bawden and Pirie that, even though infectivity is lost, the antigenic powers of the virus are retained. It might be that HN_2 would be an excellent agent for the creation of virus mutants capable of inducing the formation of antibodies without serious infection, an interesting field of study for those who work with poliomyelitis.

In recent months studies have been made by Tatum and his associates at Yale on the effect of HN_2 in causing sex-linked mutations in Neurospora. This organism, ordinary red bread mold, has both vegetative and mating forms. It is a surprisingly competent cell in that it can manufacture by synthesis from ammonia as a source of nitrogen and sugar as a source of carbon, all of the components it needs for existence, except biotin. If mutations are induced in this material by the conventional agents, such as x-rays or ultraviolet light, strains of Neurospora result which are unable to carry out to completion one or the other of the many essential syntheses done so easily by the parent form. Hence the organism, planted on the sample media adequate for growth of the original form, is unable to grow unless there is added one or the other product which would have been made had the synthetic mechanism not broken down. This provides a beautifully simple and rapid technique for demonstrating mutations and for establishing the precise nature of the change. It is found that each enzyme required for the chemical activities of the mold, is manufactured by a single gene. When the wild strain, completely competent mold, is treated with HN_2, a variety of less competent, mutant forms result, unable to manufacture vitamins and amino acids and to carry out other chemical processes.

No clear explanation is at hand as to how the nitrogen mustards interact with the constituents of genes to bring about mutations. There is good evidence that genes are composed of desoxy-ribose nucleic acid. Studies have been made of the ability of nitrogen mustards to combine with and thereby change this substance. To date the studies are not wholly satisfactory, but certain results obtained by workers under the National Research Council of Canada and extended by Chanutin suggest that when relatively purified nucleic acid or preparations are

exposed to the nitrogen mustards, well-defined changes in viscosity and in streaming double bi-refringence result. This suggests, of course, that the nitrogen mustard has caused a fundamental alteration in the constitution of the treated material. This type of interaction may well be a most important field for future investigation.

7. *Leukopenia-producing effects.* The leukopenia-producing effects of the mustard compounds, and particularly of the nitrogen mustards, are important because of their fatal nature when these compounds are used as military toxics, and because of their therapeutic value in treating neoplastic disorders of the leukopoietic tissues.

The clinical observations on the casualties of the Bari disaster illustrate as adequately as any example can, the effects of the mustard compounds on blood formation. As mentioned previously, these casualties showed at first a moderate elevation of white blood count to the 10,000–15,000 range, followed on about the second day by a profound drop or total disappearance of lymphocytes and shortly after by almost total disappearance of polymorphonuclear forms, which was preceded somewhat by the presence of more and more immature forms in the circulation. Under conditions of moderate poisoning such as that induced by the therapeutic use of the compounds, the low point of the depression persists for from 7 to 21 days. By the end of this time relatively normal values have again been attained following the appearance of immature white blood cell forms in the circulation. The fact is striking that, even though the white blood cell count is held at levels as low or lower than are encountered in other types of agranulocytosis, manifestations of local infection or of tissue breakdown are not encountered. Kindred, of the University of Virginia, made detailed quantitative studies on the lymph glands of experimental animals treated with HN_2 and analogous compounds. There is reason to believe that precisely similar changes take place in human material, although no such complete studies have been made. The extraordinarily complete dissolution by HN_2 of the normally numerous hematopoietic elements of bone marrow is striking.

The anemia produced by the interference with hematopoiesis caused by HN_2 is not severe unless the bone marrow injury is long continued. The enduring quality of erythrocytes makes them slow to reflect interference with production and bone marrow function after treatment with nitrogen mustards.

One of the most interesting studies on the toxic effect of HN_2 on hematopoiesis as correlated with the transformation of the compound in the course of its metabolism in the body is that of Karnofsky. The fact should be recalled that the nitrogen mustards, in their metabolism, form one or more imine rings, one for each of the chlorethyl groups present in the original chemical. From the experimental data it is clear that only those compounds of the mustard or chlorethyl types which can form such imine rings show evidence of leukopenic action. Also, as mentioned before, the speed of formation and breakdown of these imine rings is known from the beautifully detailed studies of Barnett Cohen. Karnofsky, who wished to injure with nitrogen mustards a rapidly growing tumor tissue without injury to blood formation, conceived the ingenious idea of pro-

tecting a significant part of the hematopoietic tissue reserves by cutting off the arterial circulation during the period of formation and breakdown of the poisonous intermediate product containing the imine ring. This was done in experimental animals by temporary occlusion of the abdominal aorta for a period of some 15 minutes in the course of which the nitrogen mustard used was injected, metabolized through the imine form and converted into a non-leucotoxic derivative. The histological results of this experiment are dramatic. From the results it is clear that a significant degree of protection was afforded to the bone marrow, by occlusion of its circulation from contact with the toxic chemical during the period of its transient presence. This principle has been used in treating patients with nitrogen mustards in an effort to avoid the bone marrow depression which limits the amount of material which can be used in inhibiting the growth of neoplastic disorders. Adequate data are not at hand to warrant more than a suggestion that the procedure of temporary arterial occlusion may be useful in protecting part of the bone marrow.

Only those mustard compounds which form imine rings cause leukopenia in the process of their metabolic breakdown. Leukopenic activity can be correlated closely with the speed of formation of the ring. For example, Compound A, a rapid imine former, is highly leukotoxic. Compound B, a slow imine former with resultant lower concentration at any one time of the poisonous metabolite, produces less leukopenia. Compound C, by its constitution incapable of forming imine rings from its chlorethyl groups, has no power whatever to produce leukopenia.

The definition through experimental studies of the profound and almost specific effect of the nitrogen mustards in injuring lymphoid tissue and bone marrow suggested early that the substances might be used therapeutically in disorders marked by neoplastic change of those tissues. Preliminary scanning experiments were undertaken early. The best and most striking of these were carried out at the Yale Medical School. At New Haven, Dougherty is said to have made experiments with transplanted lymphosarcoma in mice. The administration of one or the other of the nitrogen mustards is stated to have caused the rapid dissolution and essential disappearance of these tumors transiently. In every instance, it is reported, growth was resumed and the animals eventually died of their disease. Since no written report of these experiments is available, it is not clear whether the tumor cells became refractory to a compound to which they were originally sensitive, or whether treatment was simply discontinued. Although there can be no question of the nucleotoxic effects of the compounds there is no evidence available at present that neoplastic cells are any more sensitive than normal cells of a similar type, providing that the rate of multiplication is roughly the same. It is indeed surprising that no really precise determinations of comparative sensitivities have been made. The fact, however, provided adequate evidence of the lack of precise information concerning the survival of normal and neoplastic cells of lymphoid and hematopoietic tissue. This should be a fertile field for investigation.

At New Haven, when favorable results in animals with tumors of lymphoid

tissue were reported, Dr. Alfred Gilman, in charge of the work there on the nitrogen mustards, decided to attempt control of similar tumors in man. A suitable case was made available by Dr. Gustaf Lindskog. This unfortunate patient had an extensive lymphosarcoma infiltrating widely the tissue of the neck and mediastinum as well as the other lymphoid organs of the body. The tumor was said to have become wholly resistant to the therapeutic effect of x-rays. Because of its rapid growth, the trachea was rapidly being compressed below a point where tracheotomy could be done, to an extent which bade fair to strangle the patient. With the permission and complete understanding on the part of the subject, an amount of nitrogen mustard was administered by vein which, if given on a similar weight basis to an animal, would have resulted in dissolution of a similar cellular structure. The mass in the neck melted away. Breathing became easy once more. Lymph nodes and spleen became smaller in size. But the effect upon the bone marrow was extreme. Lymphopenia, leukopenia, granulocytopenia ensued, with severe and intractable purpura, and eventual aplastic anemia requiring repeated transfusions. The bone marrow depression was transient, however, and disappeared within a few weeks. No further treatment was given; the tumor grew again and eventually terminated the life of the patient. A new fact had been established, however. A chemical compound was at hand which would affect adversely and cause dissolution of a lymphoid neoplasm reputedly resistant to x-rays. This was a most important observation, and has since been amply confirmed. Several other patients were treated by the New Haven group before it was disbanded because of the entry of Dr. Gilman and his associates into the military service and their assumption of duty at the Edgewood Arsenal laboratories. The studies of the therapeutic value of these compounds in neoplastic disease could not be allowed to lapse, however. Accordingly, with the permission of the Committee on Medical Research of the OSRD, the agency which had supported for the Army the studies described at Yale University, last year there was created by the National Research Council a committee called the Committee on Atypical Growth. This body advised the Army on the distribution of these military chemicals for study designed to establish their therapeutic values in civilian medicine. This work was carried on under military security for obvious reasons and was assigned by the Committee on Growth to three institutions deemed qualified because of the available clinical material, the experience of the scientific personnel with tumors of lymphoid tissue, and continued association with the chemical laboratories at Edgewood Arsenal. The three institutions chosen were the Memorial Hospital in New York, affiliated with the Cornell University Medical College, the Billings Hospital of the University of Chicago, and the medical school of the University of Utah at Salt Lake City. The three groups of observers studied in all, more than 150 patients under an agreement to pool their information and to publish their results jointly The results will appear in a forthcoming issue of the *J. A. M. A.* They have been presented before the A. A. A. S. at the Gibson Island conference of August, 1946, and have been summarized in an official report from the N.R.C. which appeared in the *J. A. M. A* issue of June 22, 1946.

In short, from the vast amount of clinical and experimental work which has been done, it is apparent that in the nitrogen mustards there is available a chemical tool by which, in the treatment of Hodgkin's disease and in certain patients with lymphosarcoma, experimental results about as good as, and not much better than, those obtained by x-ray can be caused. It is quite true that the mouse is not a very large one, and the mountain was of very considerable size. The important question, however, is how much the mouse will be able to grow in the future. This is the first mouse of this type which has ever been produced, and it might very well become the parent of a great race of new chemical compounds, one of which might be more useful than x-ray. If one chooses to be really fanciful and imagines an organization able and willing to exploit this new principle, it would develop something of importance. If this could be done, difficult,expensive and laborious though it may be, it is wholly possible that chemotherapeutic substances specifically destructive to one of the other forms of cancer tissue might be developed. There is at least ample precedent for this possibility. Time only will tell whether the public wishes to have this sort of work done.

The Bari incident has been long since forgotten by most, and World War II is history. Chemical warfare, awaited with so much anxiety, has become, with the development of atomic energy, an obsolete weapon. All the fears and the precautions, the desperate efforts and anxious hours, proved to be of only prophylactic value. Despite this fact, perhaps from the studies of the mode of action of toxic chemicals, rather more salvage for human good has been made than is the case for most of the other military arms. From actual chemical warfare no lives were lost. The only fatalities were from accidents, and they were few. The lives and suffering saved from the knowledge developed through chemical warfare may be significant. This balance on the part of peacetime gains is unparalleled in the case of other military activities.

PHYSIOLOGICAL PROBLEMS IN THE TREATMENT OF HEART DISEASE[1]

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Recent work on the endocrine control of salt and water metabolism, and the use of the catheter technique for sampling the mixed venous blood and for measuring the pressure in the right auricle and ventricle have given a much clearer picture of the physiology of heart failure than was previously held, and allowed us to develop a more rational and successful therapy. It has also shown us that congestive failure is not a single entity, and has reduced the old "forward failure" and "backward failure" controversy to the level of a law-suit over a dead horse.

The first break in the concept that congestive failure was a disease entity came with the realization that constrictive pericarditis was a causative factor totally different from the myocardial weakness or arrhythmias which commonly caused venous engorgement and dyspnea. Later came the concept of right, left and combined types of ventricular failure. Then the etiologic factors—myocarditis, coronary insufficiency, and metabolic defects such as beriberi and desoxycorticosterone poisoning received recognition, and the striking effect of aging on myocardial reserve became apparent (1). A most important recent advance is the demonstration that in certain types of heart failure there is a slight but definite decrease in peripheral blood flow which diminishes cardiac output and work, while in other types, the peripheral vascular bed remains dilated and the cardiac output high until a fatal stage of decompensation is reached (2 and 3). When hypertension, stenotic valve lesions, myocarditis or myocardial senescence are dominant factors, blood pressure is easily maintained by vasoconstriction and the cardiac output tends to fall. Such control is not effective in aortic insufficiency, arteriovenous fistulae or congenital arterio-pulmonary shunts or in the presence of bone diseases such as Pagets (4) or hyper-parathyroidism which create uncontrolled hyperemic zones of great extent, or with arterial anoxia due to pulmonary disease such as emphysema, or with severe anemia or metabolic defects such as beriberi or Graves' disease, or in febrile illness. In this latter group of cases, the loss of myocardial efficiency is far less marked than in the former, for any given degree of symptomatology. In the cases with diminished cardiac work, symptoms, except for weakness or dyspnea on exertion, do not occur until the myocardium has become very inefficient. Any agent which restores part of the lost efficiency will have a striking effect in relieving the patient. In the cases with high cardiac output or work, symptoms may become severe while the myocardium still retains most of its efficiency,

[1] Presented as part of a series of lectures entitled Recent Advances in Therapy, at the Blumenthal Auditorium, The Mount Sinai Hospital, New York, on December 18, 1946.

and treatment directed at restoring efficiency is relatively unimportant so long as the overloading persists. The relative ineffectiveness of digitalis in this last type is well-known.

It should be stressed that arterial hypertension imposes little work on the heart. The increase in mean pressure is rarely more than 60 or 70 per cent, while in mitral stenosis or emphysema mean pulmonic pressure may increase three or four hundred per cent (5). Since increase in cardiac output usually raises pumonic pressure with little or no effect on sysemic pressure, the right ventricle again bears the brunt of the added burden. It is therefore not remarkable that right sided failure is more often due to overloading, and less often due to simple myocardial inefficiency than is left sided failure.

One of the outstanding discoveries made with the cardiac catheter is Sharpey-Shaeffer and McMichael's observation that in some cardiacs, breathless even in the orthopneic position, a fall in venous pressure produced by bleeding or by cuffs which hold back the blood in the veins of the limbs, leads not to a fall but to a rise in cardiac output (6). This can only mean that these hearts were filled beyond the point at which increase in auricular pressure led to increase in systolic discharge. Previously it had been believed that the point of decreasing systolic discharge with increase in diastolic filling could not be reached with an intact pericardium, and therefore was merely a laboratory curiosity. It is now realized that in certain desperately sick cardiacs, bleeding or bloodless interference with venous return not only diminishes the symptoms of pulmonic and hepatic engorgement, but actually increases the output of the heart, by increasing its efficiency. In normal persons, the cardiac output rises 15-30 per cent on changing from sitting to the recumbent posture; in severe cardiacs with diminished output recumbency causes no rise, and may even cause a further fall in output. Exercise and digestion have the same effect on output as does recumbency. It has long been known that while moderate exercise has very little effect on the systemic venous pressure in normals, it leads to a rise in venous pressure in the early mild cases of heart disease in whom cardiac output and basal venous pressure are normal; in severe failure of any type venous pressure rises markedly on effort, and cardiac output may rise, or fall.

McMichael (7) has confirmed the observation that digitalis decreases both venous pressure and cardiac output in normal men, while it raises output at the same time that it lowers venous pressure in some cases in heart disease. He was struck by the resemblance of the effects of bleeding and of digitalis and concluded that digitalis in heart failure acts solely by diminishing venous tone. This may well be true of the cases in advanced low-output failure, those in whom rise in venous pressure causes a further decrease in cardiac output. It obviously can not be true in ambulatory patients whose cardiac output rises with exercise or recumbency. In the latter group the disappearance of gallop rhythm, or a rise in vital capacity and definite clinical improvement may be caused by digitalis, and in such cases the only site of action must be in the heart. That digitalis has a beneficial effect on the function of the myocardium in failure is thoroughly proved by work on isolated hearts and on isolated strips of heart

muscle. The catheter technic permits observations only of the immediate effect of intravenous digitalis preparations. The shortening of systole and lengthening of diastole which the drug produces in many failing hearts probably permits a gradual recovery of the muscle. This will be reflected by fall in pulse rate and improvement in the circulation which only become apparent many hours after full digitalization.

It is noteworthy that in constrictive pericarditis and in cor pulmonale McMichael (8) was able to demonstrate that digitalis lowered venous pressure and cardiac output just as it does in normals, in spite of the fact that the liver and great veins were already distended with blood. This proves that the peripheral action is important even when blood volume is high and the central venous reservoirs are full, and hence that the effect in reducing venous tone may be significant in many cases of severe heart failure.

In all types of heart failure there is a disproportion between the output of the heart and the flow of blood necessary to satisfy the circulatory needs of the body. When this comes on acutely, as in severe tachycardia of ventricular origin or in massive infarction, shock with normal or slightly raised systemic venous pressure and with pulmonary edema may occur. Weakness, pallor, or loss of consciousness may precede the signs of pulmonic engorgement. With prolonged bouts of auricular tachycardia, where the initial signs of shock are less, some days may lapse before pulmonic and hepatic engorgement and edema of the legs develop into the full-blown picture of congestive failure. With more gradual development of failure, nocturnal dyspnea may be the first symptom in sedentary people, dyspnea on exertion in those leading more active lives. But regardless of etiology and speed of onset, and regardless of whether the basal cardiac output in the early stages is normal or elevated, in all cases of heart failure the rise in venous pressure on effort is abnormally great, and the cardiac output on effort insufficient for the needs of the tissues.

An inadequate cardiac output sets off the mechanism for increasing venous return and blood volume which is normally brought into play by hemorrhage, or by loss of fluid and electrolytes due to sweating, vomiting or diarrhea, or by severe trauma or burns. Among mammals for countless thousands of generations, these have been oft-recurring causes of a decrease in blood volume and in the cardiac output, and a complex mechanism to deal with the disorder begins to function whenever the circulatory needs of the tissues are not met. It therefore operates in man, not only in heart failure, but in those diseases in which blood volume is low,—cases of proteinuria, malnutrition or liver disease with low serum albumin levels, in chronic anemias; and in prolonged undernutrition with normal blood protein but low blood volume. When the hemoglobin level falls below 40 per cent, the total blood volume appears to decrease strikingly. An increase in plasma volume would only reduce the hemoglobin content of the blood. Presumably, low viscosity alters pressure relations and fluid reabsorption in the capillary loops. In such cases, as with low blood volume due to low serum albumin, edema forms readily and cardiac filling is maintained only by a high venous tone in the peripheral bed. Under these circumstances even a small

bleeding may cause fatal circulatory collapse, and rapid transfusion may precipitate pulmonary edema.

In all of these conditions, the most constant and striking feature is the conservation of sodium and of water (9). In many of these disorders the salt content of the sweat decreases, by as much as 50 per cent, and from the work of Conn, it seems clear that this is due to increased liberation of desoxycorticosterone by the adrenal cortex. Reabsorption of fluid and salt from the feces also becomes maximal, and the sodium loss in the urine, regardless of sodium intake, may drop below 50 mgm. per day as long as circulatory insufficiency persists; the total daily loss from the body varying from 150 to 300 mgm. unless sweating is excessive. A decrease in liberation of pitocin, the chloruretic hormone of the posterior pituitary, probably occurs, and Brun and his co-workers have shown that pitressin, the antidiuretic hormone, is liberated in increased amounts within a short time after producing a fall in cardiac output of normal men by having them upright but relaxed on the tilt-table. As Asmussen points out, the erect posture in itself creates latent circulatory failure. It is sufficient to stimulate the water-retaining mechanism. But to treat postural hypotension we must keep patients partially upright both day and night, to achieve an increase in blood volume of half a liter or more, and an obvious increase in the fluid in the intercellular spaces of the legs. Such an increase in blood volume and in tissue fluid volume causes the clinical picture of congestive failure and led to the concept of "backward failure." Now it is realized that even in constrictive pericarditis and tricuspid insufficiency, edema and venous distension are due to stimulation of the blood-forming and the salt- and water-retaining mechanisms which is a result of a decrease in the adequacy of the cardiac output. Conversely, the syncope at the onset of tachycardia may be regarded as due to the tissue turgor and blood volume being inadequate to force a rise in output from the embarrassed heart. In such cases pulse pressure and diastolic pressure rise as the venous engorgement and edema develop. What has been called forward failure is acute failure, what has been called backward failure is the chronic state, with the compensatory changes to inadequate cardiac output fully exhibited.

Stead and his colleagues have stressed the fact that edema formation may precede rise in venous pressure. They ignored the endocrine factor in salt excretion and ascribed edema formation to reduced sodium filtration rather than increased sodium reabsorption in the kidney. It is an important fact that in patients with hypertensive and aortic valve disease, edema can occur with no rise in systemic venous pressure—that is, no right heart failure or accumulation of blood in the great veins. Reichsman (10) stressed the fact that venous pressure may rise before edema formation, when digitalized mitral fibrillators are taken off digitalis. In such patients, only recently compensated, blood volumes may be adequate to permit a rise of venous pressure as the effect of digitalis on venous tone wears off, and before the cardiac output falls to a critical level and fluid and salt retention begins. These are cases in which right ventricular failure occurs before that of the left side of the heart, so that systemic

venous pressure rises before the cardiac output falls. The observations of Stead and of Reichsman are both acceptable, their theories are incomplete.

We may now try to consider these findings in terms of therapy. Early in our management we determine the etiologic factors, and if possible deal directly with these. To overlook Graves' disease, beriberi, arteriovenous fistulae, or constrictive pericarditis is to doom the patient to an avoidable catastrophe. But even earlier, we must estimate, from skin temperatures in the hands and feet, from the pulse-pressure, and from the vigor of the heart beat whether cardiac output is elevated, or is reduced. In the presence of cyanosis due to chronic emphysema, or pallor due to anemia, or any acute cardiac damage, reduction of blood volume or of venous return may cause severe systemic symptoms. We must not bleed or use digitalis unless the absence of such factors has been proved. There is no routine treatment of heart failure; there can only be treatment of the patient, based on the etiologic and physiologic problems he presents and the conditions of life which he must face.

When arrhythmia is an outstanding feature, its treatment by digitalis or quinidine must be pushed cautiously but thoroughly and not too slowly. This is a chapter in itself, and will not be dealt with except to stress that with rates over 180 the heart muscle is subject to ischemic injury, and quinidine must be pushed rapidly in paroxysmal tachycardias with high rates. In fast fibrillators with mitral stenosis, I prefer to begin with digitalis and usually make no attempt to restore normal rhythm unless the lesion seems to be predominately insufficiency, from the physiologic criteria of loud systolic murmur and marked auricular and apical pulsations.

In severe failure with low pulse pressure, large liver and normal hemoglobin, removal of 600 to 800 cc. of blood is the most effective immediate therapy, and femoral bleeding is easy when arm veins are collapsed and the limbs cold. Bleeding also may be invaluable in less urgent conditions where the blood volume is obviously great and cardiac output not high. Diuresis may not occur until after venesection in such cases. It must be emphasized that bleeding increases cardiac output in these cases by relieving the distended heart. The only emergency therapy of value except venesection is oxygen, preferably from a pressure mask if pulmonary edema is present. Prompt digitalization with intravenous doses of glucoside takes two hours, if divided doses are used to avoid overdosage, even with ouabain which can be given at half-hour intervals. Divided doses of digitoxin should be given at two hour intervals, digoxin and lanataside at one hour intervals in order to judge the effect of the drug. I begin with half the expected full dose because this may be enough to cause coupled beats, and then give quarter doses (0.1 mgm. in the case of ouabain) until therapeutic effectiveness or toxicity occur. But I expect no miracle from digitalis in every case, and believe it possible to prove its effectiveness in less than half the patients with apex rates of 100 or less, whether fibrillators or regular. That it has beneficial effects in some of the others I do not doubt, but the value is not comparable with that of bleeding or of the mercurial diuretics. The latter are the mainstay in drug therapy, for they paralyze the mechanism for sodium conservation. Other

diuretics get out water, but as they remove little sodium, the patient quickly regains his weight. Water ad libitum should be allowed the patient on low salt diet and mercurial diuretics, and the daily caloric intake should be kept about 1200 calories, except in obese patients, until severe failure has been controlled. In the obese, 800 calories, half from protein are preferable.

We encourage early ambulation and sitting up at meal-time, but also advise the patient to lie as flat as possible for as much of the day as he can in comfort. The erect posture, long maintained, leads to salt retention even in normals and predisposes cardiacs to nocturnal dyspnea. Rest in the middle of the day and again before the evening meal is advisable in all chronic cardiacs to effect redistribution of blood and a maximal basal cardiac output at more frequent intervals than occurs when people are up all day. But sitting in a chair is more restful than the orthopneic position in bed, and even early in recovery short intervals of sitting improve the physical condition, minimize the risk of phlebothrombosis and seem not to retard recovery or diuresis. By reducing venous return the work of the heart is temporarily reduced and the salt retaining mechanism does not seem to be stimulated by short periods of sitting or standing.

The commonest medical failures today are in the management of the ambulatory cardiac and the ambulatory diabetic. Both should be reduced to muscle and bone, with minimal panniculus; both should be on relatively low protein intake, to reduce the specific heat production and metabolic work due to protein. But cardiacs and diabetis need adequate amounts of protein to protect the liver. The diabetic should be kept with a normal blood sugar and cholesterol; the cardiac who has a normal basal cardiac output, should be kept with a normal blood volume and in negative sodium balance as long as he has any edema, or any symptoms of congestion of the lungs. This means that both diabetic and cardiac must learn to put up with some measure of privation and even weakness in order to retard, to the fullest extent, the progress of the disease. Today the doctor usually compromises and exchanges the day to day comfort or convenience of these patients for months, or perhaps for decades, or life.

Since July, 1944 we have used rice, fruit juice and sugar as the main dietary items for congestive failure, for acute nephritis, for ascities without parenchymal liver damage, and for hospitalized hypertensives. Milk and eggs and butter have no place in the diet of hypertensives, or of adults with coronary disease. All store-bought bread-stuffs, cakes, crackers, candies and breakfast foods must be eliminated—they reek with sodium. Many foods, such as cottage and grated cheese, can be desalted by prolonged washing in running water; meat and vegetables of the leafy and root types can be desalted by twice boiling after dicing. Potassium chloride, with a touch of ammonium chloride, can be used to give a pleasant salty taste to many foods. Grains, flour, nuts and beans are relatively low in sodium; sago, tapioca and unsalted spaghetti are almost sodium-free. But however you try it, getting a diet with less than 500 mgm. of sodium is very hard on all patients and impossible for most wage-earners. And if the daily sodium loss is only 400 mgm., the patient will put on a liter of edema fluid every month on a 500 mgm. intake. On a 1 gm. intake, he will

put on a liter every five days. Reduced salt intake and mercurial diuretics are the present unsatisfactory solution of the dilemma. It is hoped that desalting techniques can be developed which will permit the removal of sodium from the body through the feeding of insoluble emulsified sodium absorbents, thus making injections and toxic reactions unnecessary hazards in the management of chronic cardiacs. Cationic exchange resins offer promise in this direction. Diets with acid ash, and salt content over 1500 mgm. per day, can not be expected to reduce edema in severe failure, but even such regimes are effective in controlling many ambulatory patients, and permitting them to dispense with mercurials, or greatly reduce the frequency of injections. We have observed the use of pitocin, and found that it has some effectiveness in various types of edema, but it can not equal the mercurials in effectiveness.

To summarize:—the cardiacs with high basal levels of cardiac output, due to pulmonary, hemic, or vascular disorders, can be managed to some degree with oxygen, rest, sedation and may be cured by correcting the underlying cause of the excessive blood flow; they respond only occasionally to digitalis, and usually should not be bled.

Cardiacs of all types, but particularly those who have not had abnormally high blood flow usually respond very well to regimes causing a negative sodium balance, that is, to diet and mercurial diuretics. Those with normal basal cardiac outputs may respond to digitalis and do well on this drug for many years. In emergencies they may be quickly relieved by bleeding, or by pressure breathing with oxygen.

The chief problem today is the maintenance of a low sodium intake and at times a negative sodium balance in the chronic cardiac able to earn his living or to enjoy an ambulatory existence. The clinical picture of congestive failure is essentially the result of compensatory mechanisms which increase blood volume and venous return; the symptoms can be controlled if the basal cardiac output is normal or less than normal by reducing blood volume and by maintaining normal body weight by diet and other methods of lowering sodium available to the body. Death from this type of congestive failure, like death from diabetic coma, is now preventable, but life may be so restricted as to make wage-earning impossible in the severe cases.

Future progress depends on dealing with the myocardial defects which underly most cases of heart failure. Of these our understanding is almost as rudimentary today as it was in Withering's time, when man first found a drug capable of staying or even reversing the course of congestive failure. The investigator of heart disease faces a large and presumably fertile territory which has barely been scratched by the rude tools of the pioneers.

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THE OPERABILITY OF MALIGNANT PULMONARY NEOPLASMS WITH SPECIAL REFERENCE TO CANCER OF THE LUNG[1]

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The main part of the discussion on operability will be concerned with cancer of the lung. With improvement in operative technique and methods of anesthesia, and reduction of infection achieved by the administration of sulfa drugs and penicillin the mortality in recent years following surgical eradication of cancer of the lung no longer is the high mortality of an earlier period. Furthermore it bids fair to reach a decidedly low level with the solution of two problems: that of post-operative pulmonary embolization and that of infection of the remaining lung—which still stand in the way of a truly low mortality. Evidently therefore, the question of the operability of cases of cancer of the lung no longer is one of theoretical interest but one of vital clinical import. The pessimism which attended the thought of surgical consideration for pulmonary cancer belongs to the past and can exist at the present time only in the minds of the uninformed. Only the uninformed, maintaining that surgery offers but little, and at great danger to life, turn to useless radiotherapy for the treatment of cancer of the lung and not infrequently thereby condemn patients to treatment for such long periods that operability becomes converted to inoperability. Radiotherapists should be urged to refuse to treat patients with cancer of the lung (except for the relief of pain) until inoperability of cases has been established by those competent to do so and until there is evidence of results to be achieved by newer methods of radiotherapy.

The operability or probable operability of cancerous pulmonary lesions means of course the likelihood of complete surgical eradication of the disease whether by lobectomy or by partial or complete pneumonectomy. It means, in other words, the likelihood of a favorable ultimate prognosis. This brings us to the criteria of operability concerning which there is no unanimity of views at the present time. There are those who base operability largely on the supposed grades of malignancy (Broder's classification), according to microscopic features. There are many and perhaps most who regard tumors involving major bronchi and thus accessible to bronchoscopic diagnosis as the operable group, the peripherally situated tumors being generally regarded as unfavorable for eradication because of the likelihood of metastases. There are those who extend operability to cases in which there is cancerous involvement not only of hilar but also of mediastinal nodes in the belief that a "radical" dissection of these nodes together with removal of the affected lung may lead to cure. Finally there are to be added those who believe that the question of operability cannot be weighed or determined in advance and should be settled by an exploratory thoracotomy unless cases are patently and obviously inoperable.

[1] Lecture given at the Graduate Fortnight of the New York Academy of Medicine on October 17, 1946 at the Blumenthal Auditorium of the Mount Sinai Hospital.

I shall discuss the criteria of operability which we at this clinic believe to be worthwhile according to our observation and experience. As long ago as 1934 Rabin and I set forth a topographic classification of cancer of the lung and its application to the question of operability. At that time the study was based largely on patients who were not subjected to operation and the question now is whether the criteria of operability set up in 1934 have stood the test of time in the decade more or less of operative treatment.

The conclusions that were reached from a study of 250 cases of primary cancer of the lung in which 100 autopsies were performed can be stated briefly for it was found that only the gross topographic features were of aid in the classification of probable operability or probable inoperability.

Two main groups of pulmonary cancer were defined, the circumscribed with more or less sharp delimitation of the growth and the non-circumscribed or diffuse. The circumscribed cancers, comprising about a fourth of the cases, occupied the parenchymal and peripheral zones of the lung and were named accordingly—"parenchymal cancer" and "peripheral cancer." The latter could usually be identified as being derived from branch bronchi and were therefore also termed "branch bronchus circumscribed tumors." Although blood borne metastases were by no means rarely encountered in cases of circumscribed cancer of the lung the significant fact was that regional lymph-node involvement either was absent or usually occurred late and to a limited extent. Indeed there were instances in which the pulmonary tumor reached enormous proportions by the time patients died and yet at autopsy the hilus was found to be free from lymph-node invasion.

The non-circumscribed cancer of the lung to which three fourths of the cases belonged comprised lesions growing from main and branch bronchi and accordingly were termed "main bronchus" or "branch bronchus non-circumscribed tumors." Regional lymph-node involvement was common and often was extensive. Bearing in mind the fact that most of the 250 cases on which the study was based antedated the period of radical surgery a fair assumption was that such common and extensive lymph-node involvement or other evidences of local extension (to the pleura, etc.) would not be anticipated in the era of surgical eradication of pulmonary cancer. That our experience unfortunately has not in general been in keeping with this assumption will be stated shortly.

The x-ray features were found to comprise the main basis for distinguishing between circumscribed and non-circumscribed tumors. Surgically removed tumors or those observed at autopsy generally confirm the interpretation of the films. Sharply demarcated round shadows situated anywhere within the pulmonary fields, occasionally presenting a fluid level, characterized parenchymal tumors. Branch bronchus circumscribed tumors (also termed peripheral) cast well defined shadows extending to the surface of the lung, widening to reach the chest wall, with occasional erosion of the overlying rib or ribs. The shadows due to these tumors usually were readily distinguishable from those of atelectases. The x-ray features of non-circumscribed cancer of the main and branch bronchi were of course characteristic in the presence of broncho-

stenosis. In the absence of the latter there were infiltrating shadows most dense at the root with streaks and nodules towards the periphery, and often shadows of enlarged mediastinal lymph-nodes. In other cases the x-ray appearance was that of lymphangitic carcinosis or of pleural effusion. At times the film was virtually negative.

The subject of symptomology has no place in this discussion and is referred to here only in connection with bronchoscopy. Characteristically the parenchymal tumors are more or less silent, the peripheral and branch bronchus circumscribed growths are attended by thoracic pain and bronchoscopy is negative in both. Thus one may say that negative bronchoscopy may be a feature of operability. However there have been instances in the present surgical period of positive bronchoscopy in cases of circumscribed tumors. The reasons are not far to seek. Perhaps the most recent experience (some three weeks ago) is as good an illustration as any. A middle aged man who had been perfectly well suddenly experienced a brisk hemoptysis. An oblique film revealed a circumscribed shadow in the left chest adjacent to the cardiac shadow. Bronchoscopy revealed a lesion in a branch bronchus which from the viewpoint of the bronchoscopist was an endobronchial lesion in a position decidedly favorable for surgical eradication. At operation the tumor was typically circumscribed, its position requiring pneumonectomy. Dissection of the specimen revealed an exquisitely circumscribed cancer which had extended to and eroded a branch bronchus of the lower lobe because the bronchus was in the line of expansion of the growth. However the tumor was not derived from the interior of the bronchus and the symptom of hemoptysis was not an early but rather a late and so-to-speak accidental manifestation. The regional lymph-nodes removed with the lung were all examined and found to be free from involvement. Unfortunately a substantial vein within the specimen was the seat of carcinomatous invasion so that blood borne metastases may have already occurred. Otherwise the ultimate prognosis is excellent in this type of case.

Turning to the symptomatology of non-circumscribed cancer of the lung in relationship to bronchoscopy, the symptoms may be referable to ulceration within the bronchus, to broncho-stenosis, to pleural involvement or almost solely to metastases to lymph-nodes (or metastases elsewhere). Bronchoscopy is usually positive but may not reveal tumor tissue in a bronchostenosing lesion of an upper lobe. On the other hand bronchoscopy may be positive only as the result of the removal of tissue from a non-ulcerated area of thickened mucosa in non-stenosing lesions. Such sub-mucous extension of carcinoma may reach the level of the carina or even higher, an important point brought out by Rabin, and may thereby establish inoperability when revealed by the bronchoscopist.

I shall now put to the test of surgical experience the classification on operability which has been outlined. The only reference to be made here to mortality of operation is to say that it has been possible to follow a fair number of cases only in the past 3 or 4 years, the period of relatively low operative mortality. Obviously, therefore, no definite statement can be made on end results after surgical eradication in relationship to either circumscribed or non-circumscribed

tumors. The observations on operability can only be based on the presence or absence of involved lymph-nodes in the specimens of removed lungs or at autopsies of operated cases in which lobectomy or pneumonectomy was performed. It can be stated at once concerning exploratory operations in which inoperability was revealed that circumscribed cancers comprised a disproportionately small percentage of the cases. Furthermore, of interest is the fact that most of the circumscribed tumors were rendered inoperable not because of regional node involvement but because of fixation to and invasion of the thoracic parietes usually in the paravertebral region. By way of contrast inoperability of main or branch bronchus tumors (non-circumscribed lesions) usually was due to too extensive regional and mediastinal lymph-node involvement. Although the foregoing is true by and large exceptions occur. Thus a pneumonectomy was performed for a well circumscribed parenchymal type of cancer of the lung. Although the patient's condition was regarded as fair before operation, there was rapid deterioration after operation and death soon supervened. At autopsy there was no leakage or infection but a most extensive cancerous involvement of the mediastinal and retroperitoneal nodes as well as malignant invasion of other organs.

The data to be presented are based on an analysis of 83 cases of pulmonary cancer in which surgical eradication was attempted or performed on the assumption of operability. Forty-eight were of the circumscribed or peripheral variety, thirty-five of the non-circumscribed, main bronchus-tumor type. The difference between the incidence of presumably operable lesions and the accepted three-fourths to one-fourth ratio of main bronchus to circumscribed type is at once apparent. Indeed far fewer main bronchus than circumscribed tumors came up for surgical consideration. I may add that bronchus tumors comprise the great preponderance of cases which came only to exploratory thoracotomy and chest closure because of inoperability.

The extent of cancerous involvement, if any, of the hilar lymph nodes in the 83 cases subjected to surgical eradication is of interest, particularly in relationship to the topography of the tumor. The classification of circumscription versus non-circumscription is being reviewed at the present time but it can be said provisionally that in the 48 circumscribed cases the nodes were involved in 9 cases—to a minimal extent (one or two nodes) in 6, and pronounced in 3. Of the 35 non-circumscribed cases the nodes were involved in 18—to a slight extent (again one or two nodes) in 6, pronounced in 12. This striking contrast holds although it is realized that hilar node involvement is not the sole test of operability and also that the extent if any of more remote involvement may not be known at the time of operation. Thus there are cases of mediastinal node involvement, in the absence of hilar invasion, in circumscribed as well as in main bronchus tumors. This evidence has come to light in various ways and has been reflected in the late results. I refer here to some interval or late results only in relationship to regional node involvement at the time of operation. There are 9 patients who are well 2 to 7 years after operation for circumscribed tumors and in none was there hilar lymph-node involvement. In about the same

period there are 3 cases of pneumonectomy for main bronchus cancer that are well; of these 2 had involvement of a single hilar node. These cases are as yet far too few in number for generalizations to be drawn.

Only brief reference can be made here to the question of operability of other malignant tumors of the lung. My remarks will be confined to bronchial adenoma which has undergone malignant degeneration and to sarcoma. Concerning the former it should be noted that the lesion may remain operable even in the presence of regional lymph-node involvement because of the peculiar fact, pointed out by Otani, that the involved nodes, which may reach enormous proportions, are invaded by contiguity. Of special interest in connection with the discussion on cancer of the lung is the additional fact that the bronchial adenoma which has undergone malignant degeneration retains its usual circumscribed contour in most of the cases which have come under observation. The corollary appears to have been that they also retained operability despite even tremendous adjacent lymph-node involvement. By way of contrast I recall one or two cases in which the conversion of the bronchial adenoma was in the form of a diffuse malignant tumor which invaded the mediastinum and was thereby rendered irremovable. This was also true of a related case of cylindroma of the bronchus.

Sarcoma of the lung has also been seen in a circumscribed as well as a diffuse form. The latter, with invasion of lymphatics and lymph-nodes, has been found in most of the cases. By way of contrast there was one case of circumscribed sarcoma of the lung in which large nodes at the hilum were encountered at operation. When frozen sections from several of them did not reveal malignancy pneumonectomy was performed. It is now 10 years since operation. The patient remains well. The roentgenogram is that of a normal right lung and mediastinum. The left leaf of the diaphragm is drawn into the contracted and opaque left hemithorax.

THE EFFECT OF ATABRINE ON AURICULAR FIBRILLATION AND SUPRAVENTRICULAR TACHYCARDIA IN MAN

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AND

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The beneficent effects of quinidine in auricular fibrillation were shown by the late Sir Thomas Lewis and his coworkers (1, 2) to be dependent on several factors, namely, a) lengthening of the refractory period in atrial musculature by direct action and by decreasing vagal inhibitory influence on the atrium, b) decreasing the rate of conduction in atrial muscle, c) depressing A-V conduction. Furthermore, Lewis (3) suggested that quinidine was five to ten times more effective than its isomer, quinine, in this action.

Recently it was demonstrated by Gertler and Karp while working at McGill University that atabrine, an acridine derivative, possesses the property of paralyzing the vagal inhibitory fibres to the dog heart (6). This observation further strengthened the growing parallelism of properties between quinine and atabrine for it is well known that they both inhibit choline esterase (4), increase the coronary flow in the perfused rabbit heart (5), and depress excitability in the perfused rabbit and frog heart (7, 8, 9). To these properties may be added the curare-like action of both atabrine and quinine at the motor end plate (8, 9).

Pursuing their work still further, Gertler and Karp reasoned by virtue of the unusual parallelism of physiological and pharmacological properties between atabrine and quinidine, that atabrine would also be effective in restoring normal sinus rhythm in cases of auricular fibrillation. Experiments in the dog devised by them to test the validity of this concept bore out all their expectations (11).

Those familiar with the use of atabrine in the treatment of malaria regard the drug as virtually nontoxic in therapeutic dosage. Furthermore, as far as could be ascertained from the experimental (7, 11, 13) and clinical (14, 15) evidence, atabrine in therapeutic doses is nontoxic to the myocardium. The sole exception to this is found in the work of Smith and Stoeckle who injected massive doses of atabrine intravenously into the heart lung preparation of dogs (15). Their interpretations can be questioned in view of the fact that atabrine at such concentrations is strongly acid and that the sudden infusion of strong acid solutions may produce similar if not identical effects (16).

Thus with experimental evidence in animals as a preliminary (6, 11, 12) and with assurance that atabrine in therapeutic dosage is nontoxic to the myocardium, this study of the effectiveness of atabrine in restoring normal sinus rhythm to cardiac arrhythmias in man was undertaken.

CASE REPORTS

Case 1. History. W. B. This 55 year old white salesman was admitted to the hospital in July, 1946. He had been well until the morning of admission when he awoke with a

tender burning red area over the left malleolus, an area which rapidly spread to involve the whole leg. Fifteen and twenty years prior to admission similar lesions in the same area had been present. For three days prior to admission he had had frequent loose non-bloody stools without cramps. He felt both chilly and feverish.

Examination. The patient was an acutely ill man appearing older than his stated age. The temperature was 104.6° F. with a pulse of 80. No abnormalities were noted except for brawny red tender swelling of the left leg without cords.

Course. The patient was treated for erysipelas of the leg with penicillin and sulfadiazine. The local lesion subsided in three days, but fever, bradycardia, and diarrhea remained. Repeated cultures of blood, stool, and urine revealed no pathogens and agglutinations against all the enteric organisms were persistently negative. On the ninth hospital day, auricular fibrillation suddenly developed. Previous electrocardiograms had

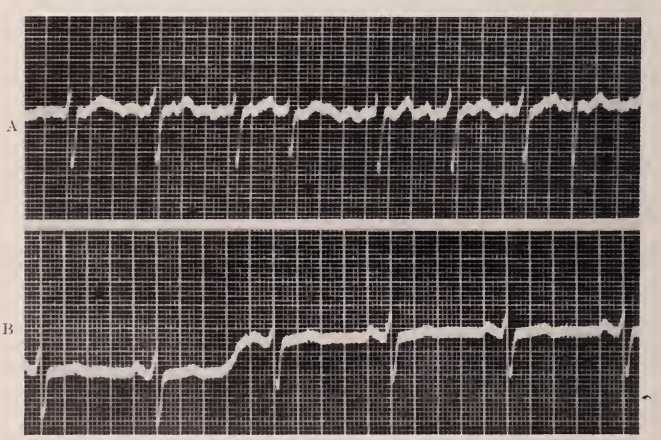

FIG. 1. A. Auricular fibrillation, ventricular rate 75–150 which was converted to regular sinus rhythm (B) with a ventricular rate of 60 by the use of 0.6 Gm. atabrine intramuscularly. All records shown are lead 11.

been abnormal. Six-tenth Gm. of atabrine in 10 cc. 1 per cent novocaine was administered intramuscularly with return of normal sinus rhythm in two and a half hours. On the twelfth hospital day a second onset of auricular fibrillation was observed. The initial dose was repeated at twelve hour intervals and two hours after the second injection the rhythm became regular(fig. 1). One-tenth Gm. orally was given thrice daily for three days and then daily for three more. By this time the patient's temperature had fallen to normal and his diarrhea had stopped. Convalescence was uneventful and he was discharged with an impression of erysipelas and of enteric fever of unknown type with myocarditis.

Case 2. History. S. G. This was the first Mount Sinai admission of an 88 year old woman complaining of dysuria, hematuria, and oliguria of several years duration. Six days prior to admission, the patient suddenly developed a productive cough associated with chills and fever. On the day of admission the patient was semi-comatosed and the history was given by her daughter. It was subsequently revealed that the woman had had recurring episodes of precordial pain and palpitations for the past ten years. These epi-

sodes persisted for twenty-four hours or longer and disappeared under therapy with ill-effects lasting for several days.

Examination. An emaciated, dehydrated woman was brought to the hospital in a semi-comatose condition. Temperature was 100.6°F.; pulse, 70; respirations, 30; blood pressure, 115 systolic and 60 diastolic. Chest examination revealed moist râles at the lung

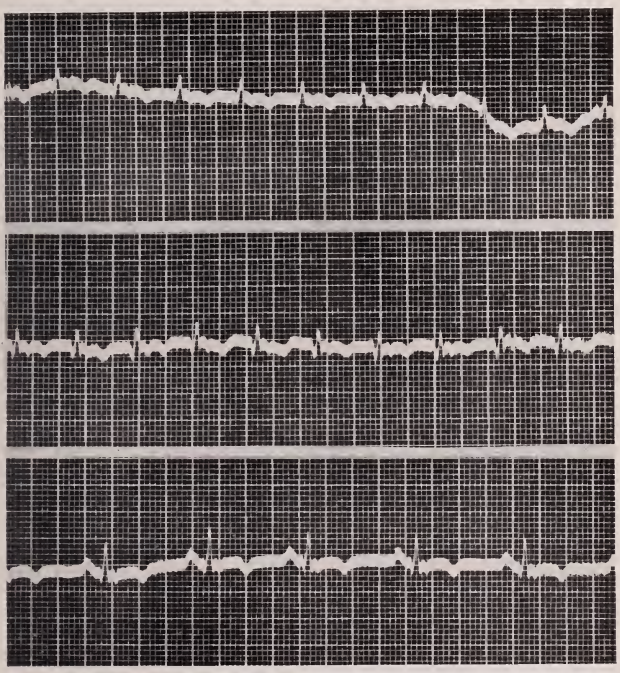

FIG. 2. A. Showing nodal tachycardia, rate 140. B. 10 seconds after the administration of 0.1Gm. atabrine intravenously. Note the prominent retrograde P wave and polyphasic QRS. C. 45 seconds after the administration of 0.1Gm. atabrine intravenously. Regular sinus rhythm, ventricular rate 75. All records shown are lead 111.

base posteriorly. The heart was slightly enlarged; the heart sounds were well heard; no murmurs or pathological accentuations were present. Abdominal examination revealed the bladder to be palpable as high as the umbilicus. Neurological examination was negative.

Laboratory data. Hemoglobin, 60 per cent with a normal differential. Urine (catheterized specimen), specific gravity, 1028; albumin, 2 plus; 10 white blood cells per high power field.

Course. A retention catheter was employed for draining the atonic bladder. Intravenous fluids, general supportive therapy and penicillin 30,000 units q.3.h. were administered. On the third hospital day, the patient suddenly developed paroxysmal supraventricular (nodal) tachycardia (fig. 2A). She was given atabrine 0.1 Gm. intravenously and regular sinus rhythm was restored within 45 seconds after the injection. The rhythm remained regular for two days at which time, the patient died from the effects of diffuse carcinomatosis.

DISCUSSION

This paper is presented as a preliminary report stressing the usefulness of atabrine in auricular fibrillation and paroxysmal supraventricular tachycardias as an alternative to quinidine. Admittedly the series is too small for conclusive remarks; but, it is nevertheless significant. At present there are on record at Mount Sinai Hospital nine cases similar to those reported in this paper in which atabrine proved to be effective in restoring regular sinus rhythm.

It was suggested by Nahum and Hoff (17) that the circus movement responsible for auricular fibrillation is the result of vagal stimulation superimposed upon an E (exciting) factor. The latter includes many conditions such as thyrotoxicosis, acute infections, and stretching of the auricular fibres during congestive failure which produces hyperexcitability of the myocardium similar to that seen in skeletal muscle and nerve under tension (18). From the foregoing it is reasonable to assume that the maximal effects of a drug in restoring regular sinus rhythm from auricular fibrillation would occur when both the vagal and E factors are at a minimum such as might occur in mild hyperthyroidism, slight infections, or early congestive failure. These latter states may be considered optimal conditions for anti-fibrillation therapy. It is interesting to note, that it was in precisely such cases that atabrine proved to be most useful. The rapidity of the action of atabrine when administered intravenously in the case of nodal tachycardia described herein, is comparable with the results obtained by Gertler and Karp in their experiments on the dog. Naturally, more cases are desirable before the usefulness of atabrine in such instances is fully established.

It is felt that atabrine may have a distinct advantage over quinidine. In intramuscular doses of 0.4 Gm., atabrine reaches a blood level of 60–220 gamma/liter within one hour and falls to levels of 60–150 gamma/liter in three hours (19). The maximal effect should therefore occur early. Thus in unselected cases of auricular fibrillation one may know in three or four hours, instead of waiting five to ten as with quinidine, whether or not response is to be expected. In such instances, search for another drug such as digitalis may be begun at an earlier hour.

The use of atabrine is to be cautioned against unless one is completely familiar with its pharmacologic and physiologic properties , for the drug is not without toxicity.

Lastly, in presenting a new type of drug for the therapy of cardiac arrhythmias, we hope to direct attention to the large group of recent synthetic anti-malarials, many with similar structures to atabrine, which may have valuable therapeutic effects on the heart.

SUMMARY

1. Two cases are reported, one of auricular fibrillation and the other of nodal tachycardia in which regular sinus rhythm was established by the use of atabrine intramuscularly and intravenously respectively. Nine cases in all are on record in this hospital to date.

2. The clinical observations are consonant with the preliminary experimental evidence.

The authors wish to express their sincere thanks and gratitude to Doctors I. Snapper and A. M. Master for their encouragement during the execution of this project.

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TUBERCULOUS FECAL FISTULA FOLLOWING PELVIC SURGERY

Case Report

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Fecal fistula complicating gynecological surgery is not rare. In Lichtman's series of 408 cases of postoperative fecal fistulae (1), there were seventy cases which followed gynecological procedures for pelvic inflammatory disease (17 cases), tubo-ovarian tuberculosis (49 cases), and for benign uterine conditions (14 cases). The injury to the bowel usually occurs by extension of the inflammatory disease to the intestinal wall or is the result of dissection of adhesions in the inflamed pelvis.

The incidence of complicating fecal fistula is highest in the tuberculosis group. In reports covering 563 cases (1 and 2) there were 67 cases of fecal fistulae following operations for pelvic tuberculosis compared to 49 cases for all other gynecological surgery. For this reason it is particularly unfortunate that the results of corrective surgery in the predominant group is least satisfactory. Mayo (2) states that using formal intraperitoneal closure 64 per cent of non-tuberculous fistulae healed; with the tuberculous variety the cure rate was only 31 per cent. The overall mortality for his group was 10.6 per cent, most of the deaths occurring in the acid-fast group.

The poor results and high mortality are readily understandable: the approach is difficult because dense fibrous tissue obliterates normal landmarks; the diseased bowel is fixed to the parietes and neighboring viscera by adhesions which must be freed before closure or resection is safe; and to add to the technical problems there is always the increased danger of flareup and secondary infection in these patients. Surgical shock and suppuration (3 and 4), naturally, are the most common causes of death, for these are the hazards of extensive surgery in poor risk patients. Thus the surgeon is faced, on one hand, by the type of fistula in which eradication is not always successful even with the most satisfactory methods, and, on the other hand, by the type of patient who does not tolerate well the type of dissection required by these methods. This problem is well illustrated by the case presented in this report.

CASE REPORT

History. (Adm. #541340) A. R., a Puerto Rican female, aged 30 years, was admitted for a fecal fistula following a pelvic operation for menometrorrhagia performed four years ago. At that time a "pus sac" was resected. Fecal drainage immediately occurred at the upper angle of the incision and continued to the present, despite an attempt at repair eighteen months after the first operation. The patient had no gastrointestinal complaints, no abdominal pain, diarrhea or constipation. Her periods were normal. She had lost no weight, nor had she cough, expectoration, fever, night sweats.

Examination. The patient was a well developed and well nourished middle aged woman. Her lungs were clear and the abdomen contained no palpable masses nor was it tender. In the upper angle of a well-healed suprapubic incision there was a small sinus draining

fecal matter. Rectal examination was negative; pelvic examination showed the uterus to be displaced to the right.

Laboratory data. Blood: hemoglobin, 76 per cent; white blood cells, 5100 with a normal differential count; blood urea 15 mg. per cent; total protein, 7.1 gm. per cent. Wasserman and Frei tests were negative. Mantoux test was positive, 1:1 million. The urine was negative; the stool showed no parasites and was guaiac negative. X-ray examination of the chest was negative. Retrograde pyelograms were normal. The barium enema was reported as showing a constant deformity of the sigmoid due to pressure from an extrinsic mass. On the right side of the abdomen there was a large mass which compressed the tip of the cecum. Barium swallow indicated no pathology in the small intestines but outlined a mass which was elevating the terminal ileum. By injecting lipiodol into the fistula, it could be traced to the sigmoid. This was confirmed by the immediate appearance, at the cutaneous end of the fistula, of methylene blue given by enema. The fistula could not be visualized by sigmoidoscopy.

Course. In view of the fact that the Mantoux was strongly positive and the patient came from Puerto Rico, pelvic tuberculosis was suspected. Uterine curettage failed to confirm this impression. Accordingly exploration was carried out (December 3, 1945) through a left rectus incision under spinal anaesthesia. Upon entering the peritoneum, the small and large intestines were found matted together by dense adhesions; in the right lower quadrant, the bowel appeared to be surrounding an inflammatory, grapefruit-sized, mass. Because of the difficulty in identifying structures, the fistula was then carefully traced through the scar towards the loop of large bowel from which it arose. During this dissection the dome of the bladder, along which the fistula ran, was opened. This opening was immediately closed in two layers. Then attention was directed towards the right lower quadrant mass. Upon mobilization, this was found to be a cystic structure arising from the broad ligament. It was resected. When, at last, the problem of the fistula could be dealt with, it was discovered that the sigmoid from which it arose was fixed deep into the pelvis and adherent to several loops of ileum. The involved loop was edematous and friable. In fact, the sigmoid in general seemed contracted. In order to mobilize enough bowel for resection with anastomosis an extensive dissection of inflammatory adhesions would have been necessary. Local pathology made this too hazardous. The sigmoidal defect was therefore closed linearly. Only one layer of sutures could be placed because of extreme tissue friability. The sutured site was drained through a stab incision. In order to further protect the suture line a spur colostomy was performed in the proximal sigmoid.

The pathologists reported the fistulous tract as showing tuberculous granulation tissue. The mass removed from the right lower quadrant was an ovarian cyst.

Postoperatively the patient did well. The colostomy was opened on the second day, the indwelling bladder catheter was removed on the seventh. The abdominal wounds healed quickly and all drainage ceased after the rubber dam was removed from the stab wound. The patient was discharged after the spur of the colostomy was partially crushed. She returned two months later. By this time the abdominal incisions were completely healed. Stool was passed both by colostomy and rectum. The patient had gained twenty pounds. Colostomy closure on March 12, 1946 was uneventful. Biopsy of the bowel, now, revealed no evidence of tuberculosis. Follow-up eight months later disclosed no bowel complaints.

DISCUSSION

The specific indications for surgery in genital tuberculosis are beyond the scope of this paper. They are adequately discussed by Jameson (3), and Norris (4) who conclude that in tuberculosis localized to the ovary, tubes, or uterus, the evidence is in favor of resection. It is not inferred that bad surgical judgment is responsible for the surgical complications. Indeed, diagnosis is extremely

difficult, even at laparotomy. Eichner (5) reports 32 cases of resection of tuberculous tubes and uteri. In only two cases was the diagnosis made preoperatively; in half of them it was not even suspected at laparotomy. The morbidity was very high: all drained cases eviscerated; one half left the hospital with draining tuberculous sinuses; and one patient developed a tuberculous sigmoidocutaneous fistula.

In the case reported above the original operation was salpingectomy for tuberculosis. Either the disease had spread to the sigmoid or that organ was injured in the dissection. A criticism might be directed against the method used in the first attempt at repair insofar as there was no temporary diversion of the fecal stream. It may be that chemotherapy will obviate the necessity of this measure in the future but it does seem more conservative to protect a suture or anastomatic line in obviously diseased bowel. By the time of the third laparotomy the viscera were matted together by dense adhesions and, unfortunately, the bladder was injured. Resection would have involved, in this case, a difficult operation carrying with it a significant mortality. It seemed much more advisable to rely on chemotherapy and defunctionalization of the loop. Rest has always been the byword of therapy in tuberculosis.

The case reported well illustrates the problem in fecal fistulae following surgery for pelvic tuberculosis. The choice lies between the more definitive procedure and one with a lower mortality. It is felt that when the local pathology is unfavorable for resection, the conservative operation is the one of choice.

SUMMARY

A case of postoperative tuberculous fecal fistula treated by a simple surgical procedure is reported. The high incidence of this complication in surgery for pelvic tuberculosis and the poor results of surgical correction are noted.

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ECHINOCOCCUS ALVEOLARIS INFECTION OF THE HUMAN LIVER

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In view of the recent invasion of France, Germany and Austria by the Armed Forces of the United States, it seems appropriate to report at this time a case of Echinococcus Alveolaris infection of the liver, which was very likely contracted by a veteran of World War I while serving with the United States Army in France in 1918.

CASE REPORT

Clinical History. (Adm. #409366, P.M. #10385) J. R., an American born white male, 44 years of age, was admitted to the Medical Service of Dr. George Baehr at the Mount Sinai Hospital, May 30, 1937. He had lived continually in New York except for a "sojourn" in France during World War I. During the period of 10 years prior to his demise, he had attacks of swelling, redness, and tenderness in the calves, ankles and knees, these attacks lasting 2 to 3 days and being associated with "fever." An appendectomy, resection of a fistula-in-ano and an herniorrhaphy had been performed at various times within the past 17 years. A gonococcal urethritis had been contracted at the age of 24. He had consumed large quantities of beer for many years. During the 2 years prior to admission, he had experienced intermittent and repeated attacks of upper abdominal cramps, jaundice and generalized pruritus lasting for several days to a week, with free periods of several months. Fever was usually present during the attacks, but was not accompanied by chills or vomiting. The day before admission he had an attack of vertigo and faintness and passed a copious bloody stool. He had had no hematemeses. There had been a loss of 11 pounds in weight in the past half year.

Examination. The patient was a well developed, acutely ill, febrile, sallow and icteric man. Numerous telangiectases were present on the skin of the face, lips and chest. The heart was found to be moderately enlarged to the left. The sounds were of good quality. The blood pressure was 92 mm. of mercury systolic and 64 mm. diastolic. The liver edge was palpable 3 fingerbreadths below the costal margin and its surface was described as hard and slightly irregular. The spleen was not palpable. A hydrocele was present on the right. Rectal examination disclosed red blood on the glove. During the 12 hours he remained in the hospital he became increasingly stuporous, profuse bleeding from the rectum continued, his jaundice deepened, shock was evident and he lapsed into coma and died. The clinical impression was that the patient had been suffering over a period of years from a chronic cholangiolitis, presumably due to common duct obstruction. The terminal acute episode was ascribed to a superimposed hepatitis. The essential laboratory findings were as follows: The urine contained 2 plus albumen, 1 plus acetone, and 3 plus bile. The icteric index of the blood was 11 (acetone method; normal 3). The Van den Bergh reaction was prompt positive, 1.5 mgm. per cent of bilirubin. The cholesterol content of the blood was 125 mgm. per cent; there was only a trace of the ester.

Necropsy findings. The autopsy was performed several hours after death. The body was well developed and exhibited a distinct icteric tinge of the skin and mucous membranes. Approximately 500 cc. of bile stained fluid were present in the peritoneal cavity; small quantities of similar stained fluid were present in both pleural cavities.

The *liver* was distinctly enlarged and weighed 2450 grams. Its superior surface was partly bound to the diaphragm by dense fibrous adhesions. Several of these adhesions were found to enter the parenchyma of the liver at the site of deep grayish scars, which

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dipped into the liver parenchyma and formed depressed areas on its surface. Its surfaces were deep green in color and distinctly granular due to the presence of small irregular nodulations. The individual greenish nodules varied in size but averaged 2 mm. in diameter and were separated from each other by depressed translucent pearly grayish grooves (capsular thickenings). Upon sectioning, the cut surface revealed a completely distorted architecture replaced by nodules similar to those described on the surface (fig. 1). The pearly gray fibrous strands made up a large portion of the cut surface. Occasionally, larger green-stained nodules of liver parenchyma were encountered, these measuring up to 1 cm. in diameter. In the convex portion of the right lobe, beneath one of the deep scars mentioned above, there was an irregular, clover-leaf shaped area, which was partially calcified and

FIG. 1. Cut surface of the liver showing biliary cirrhosis and marked dilatation of the intrahepatic bile ducts with deposition of biliary concretions. Note the narrowing of the common hepatic duct just proximal to its junction with the cystic duct.

measured 3 x 2 x 1 cm. Upon sectioning, it was distinctly demarcated from the liver parenchyma by a fibrous capsule within which there were numerous calcified concretions as well as a soft, cheesy and gelatinous yellowish gray material. It was adjacent to, and seemed to empty into, a bile duct containing concretions. Closer inspection revealed its division into individual smaller nodules each surrounded by a dense fibrous capsule. (Much fibrous tissue was present between the nodules.) Their contents were in part gritty, and included a fragmented yellowish membrane which in turn was enveloped by a gelatinous material. On cutting deeper through the largest of these cyst-like areas, its contents were found to be distinctly grayish in color and firmly gelatinous in texture, and fragments of a thin membrane coursed through it. Situated within a radius of 5 cm. from this group of nodules there were present within the superior portion of the right lobe of the liver 4 or 5 similar groups of nodules, which were of approximately similar size and structure. Some contained calcific material; one was in contiguity with a dilated bile duct containing "gravel."

In addition, there were a few isolated individual cysts, each less than 1 cm. in diameter, which were circumscribed like the others, and contained a firm gelatinous material. One cyst of this size was empty and had a smooth pale gray wall; it was situated just beneath the capsule on the superior surface.

The intrahepatic bile ducts were everywhere distinctly dilated, their walls being thickened and surrounded by dense fibrous tissue. Within the lumens of some of these hepatic ducts there were small greenish black concretions, which were easily crushed. The right and left main hepatic ducts were markedly dilated, measuring 1 cm. in diameter. Their lumens were also filled with concretions; their walls were extremely thick, and were surrounded by a collar of firm grayish white fibrous tissue measuring 3 mm. in width. Many sections through this collar showed the presence of numerous discrete golden yellow foci, each approximately 1 mm. in diameter. Just distal to the junction of the right and left hepatic ducts to form the common hepatic duct there was a sudden narrowing of the lumen, which now measured only 2 mm. in diameter. Distally the common hepatic and common bile ducts showed no gross changes. The cystic duct joined the common hepatic duct about 0.5 cm. below the stricture described above. At this point a round, firm 1 cm. sized nodule was felt, which upon section was gray and contained numerous brilliant golden yellow foci, which appeared to have cystic centers. They varied from 1 to 2 mm. in diameter. The gall bladder wall was thickened, but it contained no stones. The spleen was slightly enlarged, weighing 240 grams. The lumen of the distal ileum and the entire colon was filled with both bright and dark red blood. No bleeding points were discovered. The other positive findings were inactive rheumatic heart disease in the form of a chronic interstitial mitral valvulitis and dilatation and hypertrophy of the right ventricle, pulmonary emphysema, and a bilateral hydrocele.

Microscopic examination. Sections taken at random through various portions of the liver disclosed a similar picture. The individual lobules were uniformly and partially destroyed in the periportal zones, due to the invasion of dense connective tissue containing an abundance of proliferating branching tubular structures, so-called bile sprouts (Zwischenstücke), whose intimate connection with liver cell cords was frequently visible. The stroma of the widened periportal fields was infiltrated with polymorphonuclear leucocytes and small lymphocytes as well as occasional plasma cells. Bile thrombi were frequently observed within the bile canaliculi. Moderate parenchymal edema was present.

A general survey of the gross nodules described within the liver parenchyma as well as those in the common hepatic bile duct and periductal tissues showed a striking similarity of the histologic picture. Within the central portion of the nodule there was a folded, eosinophilic, laminated cuticular membrane embedded in a granular debris and a homogeneous acidophilic material (fig. 2). This was surrounded by a dense fibrous connective tissue layer containing cholesterol crystals. In the periphery of this layer and extending into the liver parenchyma there were scattered groups of epithelioid cells, fibroblasts, and collections of lymphocytes and plasma cells as well as a rare eosinophile. Scattered multinucleated giant cells of the foreign body type were present. In various areas there were deposits of calcium, particularly in portions of the dense fibrous wall adjacent to the hyaline cuticle. An external parenchymatous layer could not be found. One small area of membrane showed a group of low cuboidal cells on its inner aspect.

A section taken through the left main hepatic duct, which was grossly markedly dilated and showed yellow spots on section, revealed ulceration of the mucosal surface and echinococcus cyst walls in juxtaposition with the ulcerated surface and also within the fibrous wall. These showed the same detailed picture as depicted above. Serial sections of one of the loculated cysts demonstrated beautifully the continuity of the cavities of the loculations, which is best described by the German word "Ausstülpung" indicating the extrovertive or budding character of the proliferation (fig. 3). A section through the nodule in the right lobe of the liver which grossly appeared to have ruptured into the adjacent bile duct confirmed this impression and supplied the necessary evidence for interpreting the progression of the disease as originating in the liver and arriving at the porta hepatis via the biliary duct system.

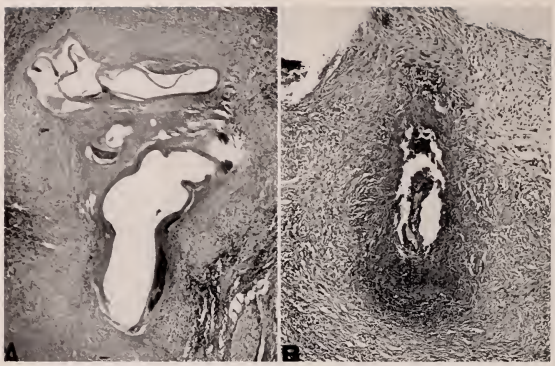

Fig. 2. (a). Section of one of the nodules showing the cuticular membrane with foci of calcification in the adjacent connective tissue. No scolices are present.
(b). Section of another nodule showing central necrosis surrounding a fragment of cuticular membrane. More distally there is extensive fibroblastic proliferation.

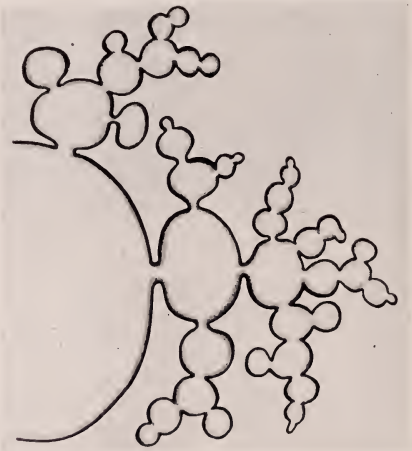

Fig. 3. Diagrammatic representation of the continuity of the loculations as determined by serial sectioning. (Copied from Jahn (9))

COMMENT

In 1856, Virchow (1), in an excellent clarification of a complex and confused subject of the time said, "*Nach dieser Schilderung kann nun wohl kein Zweifel darüber bleiben, dass die ganze Geschwulst als aus zahllosen, ungewöhnlich kleinen Echinokokkus-blasen zusammengesetzt war, und dass man dieselbe nicht mehr ein Alveolarcolloid zu nennen berechtigt ist.*" With these words Virchow gave to the scientific world a new pathologic entity, which was soon to arouse much dispute as to its relationship to the already, even at that time, well known and common, simple hydatid disease of the liver. This conflict has continued without abeyance up to the present and, as yet, appears no nearer settlement.

There are those who hold for the occurrence of two distinct taenia in order to explain the development of two distinctly different pathologic types of echinococcus disease (2). Their observations have not been confirmed by other able observers (3), who, on the other hand, support the thesis of a single species of taenia, which produces one or the other of the two forms of the disease depending upon the reaction of the body to it. Dew (4) in his discussion, makes a brief excursion into the realm of speculation and succinctly offers the suggestion that the sojourn of the parasite within the body of the ox instead of its more frequent accomplice, the sheep, so influences the subsequent character of the taenia as to evolve a partial metamorphosis in its potentialities and the production of the altered state seen in the alveolaris type of infection in the human. Although a corresponding situation has not been found amongst parasites affecting either human or animal, the knowledge that amino acid and protein constituents vary in different species of animals (5) does suggest the possibility that Dew's speculations are on the right track and may well be confirmed by future experimentation.

The pure alveolaris form of echinococcus infection has only been reported previously as developing in the North American continent by Osler in the 1906 edition of his textbook. The six cases he mentions were in people of German origin. The case of James and Boyd (6) appears to be one of hydatid infection which assumed the alveolaris form in some areas. For the most part the cases of hydatid infection reported in both the North and South American continents have been those occurring in regions where sheep raising predominated (7). This is also true of cases of hydatid infection occurring in Europe and elsewhere. But in certain regions of Europe, particularly Southern Germany, Switzerland and the Tyrol, where oxen and not sheep are herded, the alveolaris type of infection is overwhelmingly predominant (8). This supports Dew's (4) suspicion that possibly the host influences the form of the disease inasmuch as most authorities feel that it has never been proved that E. alveolaris is in any way morphologically different from E. hydatidosus.

SUMMARY

A case of Echinococcus Alveolaris infection of the liver probably contracted in France during World War I is reported.

A brief review is given of the present state of our knowledge of this disease and of its geographical distribution.

Because of the distribution of our troops in Europe during World War II a long range view must entertain the prognostic suspicion that similar cases will be encountered in the inhabitants of the United States in the future.

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ESSAYS ON THE BIOLOGY OF DISEASE[1]

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Chapter 18

CARDIOSPASM

Etiology. Although older writings are full of references to the "hysterical" and "neurotic" personality of affected individuals and to the frequency of a psychic trauma in the initiation of the cardiospasm, the psychosomatic nature of the malady was not seriously considered until comparatively recent times. Thieding (1) in 1921 was apparently the first to suggest a psychological origin since he was struck by the frequency with which it followed a psychic trauma, and that it occurred especially in individuals with neuroses. In 1926 Schindler (2) subscribed to this view and was enabled to cure early cases by psychotherapy. He also observed that the disease frequently followed an annoyance that "had to be swallowed," usually from somebody superior. Alkan (3) writes in a similar vein, and notes that relapse frequently follows some excitement. Winkelstein (4) reported 8 cases of cardiospasm following a psychological trauma; in two instances cure followed psychotherapy. He regarded cardiospasm as an exquisite example of an organic disease of functional origin. In the discussion of Winkelstein's paper Verbrycke (5) quotes the case of a patient who was relieved by dilatation but the cardiospasm recurred immediately following the robbery of his bank. Frey and Duschl (6) view cardiospasm as an organ neurosis following various forms of psychological strains, and believe that psychotherapy may effect a cure in early cases. Opitz (7) expresses himself similarly. Weiss (8) recently stressed the psychosomatic nature of cardiospasm and reported nine cases. He finds that cardiospasm follows an emotional conflict; that it often occurs during puberty in persons whose early life gives evidence of personality difficulties. Other members of the family are often neurotic. Parent-child and sibling relationships are seriously disturbed. Exacerbations occur which can be frequently correlated with fresh psychic insults. Weiss views the physical disorder as representing symbolically a compromise between the gratification of certain impulses and their rejection by another part of the personality. He holds that the malady necessitates both physical and psychological treatment. The latter is especially useful in early cases and as an adjuvant in the later phases.

As further testimony of the psychosomatic nature of cardiospasm we may cite the frequency with which cardiospasm is associated with other psychosomatic diseases. Of 42 cases collected from the records of the Mount Sinai Hospital,

[1] This is the eighteenth chapter in a series of essays by Dr. Eli Moschcowitz, in which an attempt will be made to interpret certain forms of chronic disease from the biologic viewpoint, as opposed to the current trend toward rigid classifications implying a concept of disease as a more or less static phenomenon.

According to present plans, these essays will appear in consecutive issues of the Journal of The Mount Sinai Hospital. When the publication of the projected series of essays is completed, the several installments will be assembled and printed as a monograph.—Ed.

four or 9.5 per cent were associated with peptic ulcer, usually near the cardia, two or 4.8 per cent with Graves' syndrome, one or 2.4 per cent with mucous colitis and one or 2.4 per cent with essential hypertension. The comparatively high incidence of cardiospasm with peptic ulcer is noteworthy, and has been frequently commented upon. Such cases are viewed generally as "secondary" cases of cardiospasm as contrasted to the primary variety in which "no cause" could be assigned, and is viewed as reflex in origin. We question whether this view is correct, since in a few cases that have come under our observation, the patient states that the spasm arises from fear that the ingestion of food may cause pain or distress.

Cardiospasm is the only psychosomatic disorder that occurs comparatively frequently in children and even in sucklings and this fact has been used as a refutation of its psychosomatic nature. Nevertheless the literature of pediatrics contains abundant testimony that cardiospasm frequently follows psychological trauma. Husler (9) reports and quotes a number of cases in which the cardiospasm promptly followed weaning either to the bottle or to solid food. He frequently observed this occurrence in spoiled, unruly and tyrannical children whose parents are neurotic and are protective. The child is often the only child. Treatment by suggestion or through circumspect handling of the mother is usually efficacious. Sudhues (10) collected 101 cases in children below the age of 13. Most occurred during the first or second year, and he regards cardiospasm as one of the commonest causes of vomiting in early life. He found that a large percentage of the parents were of the neurotic or hysterical type and that the older children frequently suffered from enuresis and pavor nocturnus. Lust (11), Monrad (12) and Finkelstein (13) describe cases of cardiospasm in children following suggestion incited by indiscreet remarks of parents or the insistence on their part to eat disliked foods, or a food that previously had caused some distress. These children recovered by suggestive treatment or some other form of psychotherapy. Lust reports the case of a child of 3 that was cured by hypnosis. Kelly (14) describes a number of children with cardiospasm due to psychic trauma.

The frequency of cardiospasm in infants and children is probably due to the fact that oral receptivity plays a much larger role in their motivation than it does in adults.

Cardiospasm like most psychosomatic disorders, especially Graves' syndrome and peptic ulcer, is much more frequent during wars. Abel (15) and Meyer (16) saw a large number during World War I, and Hoffman (17) observed it frequently in camps during World War II.

Inasmuch as we believe that all psychosomatic diseases are the result of two factors, namely the impact of a psychic insult upon a psychological background or constitution it would be fruitful to study the type personality that is subject to cardiospasm. Our own experience has not been sufficient to warrant a definite statement, but from our limited experience they are fearful, sensitive and extremely insecure folk who approximate the type we have previously described

as characteristic of Graves' syndrome (18). They are subject to tremors under stress, dermographia, increased sweating and turgidity of the skin. Abel and Thieding have made similar observations.

There can be little doubt that cardiospasm represents an achalasia (19) that is, the failure of the relaxation of the normal tonus of the cardia before the advancing food. The probability is also strong that this is mediated through the autonomic nervous system, but this is not equivalent to saying that the cause of cardiospasm is a dysfunction of this system, a statement frequently made. Changes in the vagus nerve have been reported by some observers, and none by an equal number. In late cases, changes in the sympathetic ganglia of the walls of the esophogus have been reported, but these are believed to be secondary, due to the profound inflammatory changes within the esophogus.

It occurs about equally in both sexes.

Course. As in Graves' syndrome, the cardiospasm may arise suddenly, as after a fright, or gradually, from a slow continuous or reiterating anxiety. At first, the spasm is intermittent; later the periods of well being become shorter and shorter, until finally the spasm is persistent, and the victim finds it increasingly difficult for food to enter his stomach. In this stage fluoroscopy shows a slight diffuse fusiform or spindle-shaped enlargement of the esophogus, with a slow trickle-like emptying of the barium into the stomach; and treatment by suggestion, psychotherapy or even hypnotism may afford complete relief. If the process continues, the dilatation becomes progressive from below, upward, and it becomes more marked in the lower two thirds of the esophogus. The patient now finds that only be forcible movements of the chest muscles can he force food into the stomach. This exertion causes pain in the lower part of the chest. In a still later stage the esophogus not only continues to dilate but lengthens forming an S shaped curve, with the redundant portion becoming so large as to fold upon the diaphragm or it may even invaginate through the diaphragm into the stomach. The esophogus in the advanced phases may hold as much as 500 cc. of fluid and under such circumstances may compress the surrounding mediastinal structure sufficiently to cause asthma-like symptoms.

Morphologically, the esophogus in the early stages is entirely normal with the exception of the moderate dilatation. In the advanced stages, there is a profound thickening of the muscular coat especially of the circular layer, which undoubtedly represents a work hypertrophy. Furthermore as the result of the stagnation of food content, inflammatory changes in the wall of the esophogus occur with edema of the mucosa and not infrequently superficial mucosal ulcerations or deep ulcers. Perforation is very rare, but lymphangitic extension of the inflammatory process may cause a chronic mediastinitis or a mediastinal abscess. Carcinoma develops in cardiospasm more frequently than the normal average, according to Fleiner (20) in 7.5 per cent. Chronic pneumonitis (21) or bronchiectasis or lung abscess (22) from aspiration of food are not infrequent. At operation or autopsy no closure at the cardiac opening is found. This only occurs during life.

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Robert K. Lambert

November 5, 1898—October 3, 1946

With the passing of Dr. Robert K. Lambert on October 3, 1946, Mount Sinai Hospital lost a brilliant, distinguished, and beloved member of its staff. Dr. Lambert's identification with Mount Sinai Hospital was ancestral. By tragic coincidence his father, also revered by those who knew him, was called from the midst of a career of devoted service at Mount Sinai Hospital at almost the same age as his son.

Born in New York City in 1898, Dr. Lambert received his early education in New York private and public schools where his popularity, wide range of interests, and high academic standards marked him for a successful career in practically any field he might have chosen. The sciences were always his dominant interest. At Columbia College, probably due to the inspiration of Professor McGregor, zoology especially attracted him and he enrolled enthusiastically in almost every course then offered by the college on subjects related to animal life and development. His interest in other fields was not sacrificed, however. A broad intellectual curiosity manifested itself early, not only in his superior rating in classical as well as in scientific studies, but also in his wide range of extracurricular interests. Dr. Lambert was not a "grind." His buoyant personality and fine sense of humor encouraged many sincere friendships that remained with him throughout his career.

Graduating with distinction from the College of Physicians and Surgeons in 1922, Dr. Lambert interned at the Mount Sinai Hospital, an association which continued for the rest of his life. Again his skill and perseverence won him the admiration of attending and house staff colleagues. There followed a profitable year of physiological study and investigation with Professor Ernest Starling in London, after which Dr. Lambert returned to New York to commence the private practice of internal medicine. As usual, he was eminently successful, in a short time developing a large following. But the scientific limitations of general practice did not satisfy him. After a few years he had had enough, and he decided to study a specialty that would permit him more time and opportunity for laboratory investigation. Not too proud to don once more the "whites" of the hospital house staff, he assumed the eye residency at Mount Sinai Hospital under Dr. Julius Wolff, graduating in 1929.

When Dr. Lambert opened his office for the practice of ophthalmology in that year, he had acquired the invaluable background of an experienced physician as well as that of a laboratory worker, and this training was always to stand him in good stead. With rare determination, he adhered rigidly to his early concept of dividing his time between clinical and laboratory work; a practice that grew with amazine rapidity was never permitted to encroach on the time allotted to the laboratory. As a result he was responsible for brilliant investigation in retinal and orbital circulation, studies which brought honorable

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mention at the American Medical Association convention in 1940. This work was initiated under the aegis of Dr. Wheeler while Dr. Lambert held the Dubois Fellowship at the Columbia Eye Institute. Other important works followed, particularly in the study of glaucoma, investigations which are now being pursued further by his associates. In recognition of his clinical acumen and of his executive qualities, Mount Sinai Hospital and Montefiore Hospital, with which he was associated, appointed him progressively to positions of increased responsibility—both in his own specialty and in committees concerned with hospital planning. At the age of forty-five, Dr. Lambert occupied the posts of Attending Ophthalmic Surgeon to Mount Sinai Hospital, Consultant to Montefiore Hospital and Clinical Professor of Ophthalmology at the College of Physicians and Surgeons.

The readers of this Journal will require no detailed enumeration of his professional honors nor of his service to his country in both World Wars. Such information is readily availabe in the more factual obituaries of thenewspapers and professional journals. For those of us who knew Dr. Lambert, it is more fitting to recall the remarkable personal attributes of his that we are certain to miss. There was, for example, the singular way in which people were drawn to him—colleagues, patients, acquaintances. It was not so much his sparkling humor or his intellectual vitality as his curious ability to draw out the other person, to understand and to sympathize with a point of view often completely at variance with his own. He was gentle, patient and a delightful companion. Nothing pleased him more than to help others with their difficulties, and he often served as councillor for his many friends.

Few successful men have been able to integrate their activities with the fine balance that Dr. Lambert achieved. His demanding private practice would have inundated a smaller person, yet he was able to cope with this deluge, supervise the functioning of the hospital Eye Service, give time to considerable post-graduate teaching and simultaneously carry out his notable laboratory work. These tasks were consummated with surprising ease. There was always ample time, too, for discussion with the younger men of their problems—laboratory, clinical or personal. Nothing was permitted to supersede what he regarded as his chief professional responsibility, the comprehensive training of younger men—instilling of the investigation spirit, and the technical training to pursue laboratory problems with competence. There was a healthy restlessness and dissatisfaction with his own work, and he continually strove to improve its already excellent quality, even to the point of exploring new and remote fields of investigation for any possible bearing on his specialty. For this year, an intensive study of electronics had been planned.

Dr. Lambert's vision helped to shape not only the Eye Service but the entire concept of the future hospital.

ABSTRACTS

Authors' Abstracts of Papers Published Elsewhere by Members of the Mount Sinai Hospital Staff

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

Carotid Body Tumor of the Middle Ear and Mastoid. H. Rosenwasser. Arch. Otolaryng., 41: 64, January, 1945.

From collective reviews it appears that to date there have been approximately 300 cases of tumor of the carotid body reported, an indication that tumors of this type must be regarded as rare. Even less frequent, however, are the reports of cases of aberrant carotid body tumor. The occurrence of a carotid body tumor in the middle ear and extending into the mastoid process in the absence of a demonstrable tumor of the carotid body in the neck, however, has not hitherto been described, and because of the extreme rarity of this condition a description of this case is warranted. Of extreme interest and possibly providing, theoretically at least, a morphologic explanation of the presence of a carotid body tumor in the middle ear and the mastoid process is the communication of Dr. Stacy R. Guild, which describes the glomus jugularis. The possibility that the tumor herein reported may have developed from the glomus jugularis is tentatively proposed.

Cold Hemagglutination and Cold Hemolysis. The Hemolysis Produced by Shaking Cold Agglutinated Erythrocytes. D. Stats. J. Clin. Investigation, 24: 33, January, 1945.

Blood containing potent (titer over 1/3000) cold hemagglutinins was readily hemolyzed if shaken in the cold. Detailed studies indicated the facts that normal blood or blood with low titers of cold hemagglutinins was not hemolyzed by shaking; as the number of erythrocytes was reduced, hemolysis diminished absolutely and relatively; the reaction of hemolysis was unaffected by complement and occurred with heat inactivated serum. Hemoglobinemia and hemolytic anemia are not invariably present in patients whose serums exhibit a high titer of cold hemagglutinins, even though such serums are capable of causing cold hemolysis in vitro. Paroxysmal cold hemoglobinuria may occur in patients with potent cold hemagglutinins. In these patients, the cold hemolysis test with tapping is positive. Paroxysmal cold hemoglobinuria in syphilitics is associated with a positive Donath-Landsteiner test and is different serologically from the cases with hemagglutination.

Clinical and Electroencephalographic Studies: The Electroencephalogram in Psychoneurotics. H. Strauss. J. Nerv. & Ment. Dis., 101: 19, January, 1945.

The electroencephalographic patterns occurring in psychoneurotics were studied with the patient at rest and during hyperventilation. They were compared with patterns of control subjects. It was demonstrated that patterns with a high amount and good continuity of alpha activity are rarer in psychoneurotics than in the control subjects and that they are particularly rare in patients with chronic anxiety and difficulties in adjustment. The theoretical implications and the practical value of these observations are discussed.

Intern Selection: Wanted, an Orderly Plan. J. Turner. J. A. Am. M. Coll., 20: 26, January, 1945.

The present situation in intern selection is chaotic. Internships are now being awarded early in the third year of the medical school training, and the trend toward earlier selection is continuing, even into the second medical school year. Students are being pressed into

early acceptance by some hospitals, at the risk of losing the offer of internship. No method has been devised so far which corrects the faults in the present situation or which meets the particular problems of the medical students. An orderly plan is presented which is applicable on a nation-wide basis, which substitutes order for present disorder, which shows how interns may be selected with fairness to all after completion of three years of medical school work, and which provides a means by which students may exercise a choice of the best internships which they can earn on merit.

Volume Dosage in Radiotherapy. B. S. Wolf. Am. J. Roentgenol., 53: 77, January, 1945.

With the international adoption of the "roentgen," measurement of X-ray and gamma beam intensities in air was put on a practical basis. It also became possible to express the ionization in small air cavities within tissue equivalent materials in terms of the "tissue roentgen" and several investigators published depth dose curves for various clinical combinations of radiation beams and fields. From these data, it is possible to calculate the ionization within tissue and to approximate the actual energy absorbed by a given mass of tissue. The biological effect produced is probably most directly related to the amount of energy absorbed by a given quantity of tissue, provided a correction factor for variations in ionization density is introduced. It is important to note that little biological or clinical effect is to be expected even though large amounts of radiation energy is delivered to tissue unless significant amounts of energy are absorbed from the beam by the tissue. Several British investigators have published theoretical and experimental data on energy absorption by tissue. This paper draws attention to this phase of radiation dosimetry which has received little emphasis in American publications. The method of calculating energy absorption devised by Happey and Ellis is modified: for a given thickness of tissue, a factor F is obtained fom a graph which, when multiplied by the area of the field and the dose (measured in air), gives the approximate energy absorption. The result is expressed in "c.c.-roentgens" or "gram-roentgens." The conditions under which such calculations may be of importance are discussed.

Effect of Liver Disease on Vitamin A Metabolism. D. Adlersberg, H. Sobotka and B. Bogatin. Gastroenterology, 4: 164, February, 1945.

Profound changes of Vitamin A metabolism were found in liver disease. Severe hepatic damage was associated with low vitamin A blood levels and lack of elevation in the tolerance tests ("flat curves"). The changes of the vitamin A metabolism were correlated with the clinical course and various liver tests, and proved to be of diagnostic value in the follow-up of liver disease. Clinical improvement is accompanied by the gradual return to normal levels of vitamin A in the blood and to normal or even abnormally high tolerance curves. Poor response in the tolerance test may be explained by diminished hepatic reserves or by disturbed intestinal absorption of vitamin A. Enzymatic systems, essential for the intestinal absorption, are controlled or influenced by the liver and are probably impaired by liver disease.

Congenital Ileal Atresia with Gangrene, Perforation and Peritonitis in a Newborn Infant. E. E. Arnheim. Am. J. Dis. Child., 69: 108, February, 1945.

A case of congenital atresia of the ileum with gangrene, perforation and peritonitis in a newborn infant is reported. This is the twelfth reported cure of atresia of the intestine below the duodenum and the second cure of a patient in this condition when perforation and peritonitis had supervened. The surgical plan was that of staged operations, consisting of obstructive resection, ileocolostomy and excision of the exteriorized ileum.

Use of LSV for Evacuation and Care of Amphibious Combat Casualties. A. Kaplan. U. S. Nav. M. Bull., 46: 289, February, 1946.

A description is given of how the L.S.V. (landing ship vehicle) was converted for the care and evacuation of combat casualties during the early assault combat phase. A sketch is

shown of the various sections on the vehicle deck and how the facilities were arranged to accomodate conveniently 350 litter patients and 500 ambulatory patients.

Strophanthin Treatment in Angina Pectoris. B. Kisch. Exper. Med. & Surg. 3: 1, February, 1945.

In cases of angina pectoris due to coronary sclerosis, a treatment with Strophanthin and Aminophyllin administered intravenously has proved to be the most effective one. This statement corroborates the experiences of other physicians like König, Edens, etc.

Distribution of Proteoses and Peptones After Intravenous Injection. B. Lustig, A. R. Goldfarb and D. Adlersberg. Proc. Soc. Exper. Biol. & Med., 58: 120, February, 1945.

The investigation was concerned with the distribution of proteoses and peptones, labeled with N15, in the mouse after intravenous injection. N15 was rapidly removed from the blood stream and was found after ten minutes principally in skin and carcass, while the remainder was accounted for in the gastrointestinal tract, liver and urogenital tract. Thirty to 180 minutes after injection, progressing amounts of N15 were found in the excreta, the predominant portion, however, still remained in skin, carcass and gastrointestinal tract. There is evidence of absorption of intravenously injected N15 into the gastrointestinal tract throughout the experimental period of 3 hours.

Psychosomatic Aspects of Stuttering. B. C. Meyer. J. Nerv. & Ment. Dis., 101: 2, February, 1945.

The writer's findings were based on an examination of one hundred and sixteen stutterers at the National Hospital for Speech Disorders in New York. Although stuttering in the families of these patients occurred nearly ten times as frequently as in the families of non-stutterers, there was no proof that stuttering is inherited as such. Environmental factors could not be discounted in the majority of instances. The only significant physical findings noted consisted of somatic expressions of anxiety: tendon hyper-reflexia, dilatation of the pupils, increased sweating etc. Psychologic studies revealed that the stutter is but one manifestation of a general neurotic problem. Many patients provided a history of nail biting, bed wetting, nightmares, palpitations and other expressions of anxiety. The writer views stuttering as a neurotic conflict between a conscious will to speak and an unconscious inhibition of speech. His findings failed to support the shift-of-handedness theory of the causation of stuttering. Criticism is offered concerning various physiological, chemical and electroencephalograpic data which have been cited as important determinants in the phenomenon of stuttering. In view of the psychologically defensive character of the symptom indiscriminate attempts to cure stuttering as an isolated phenomenon may lead to disastrous consequences.

The Production of an Antibiotic Substance Similar to Penicillin by Pathogenic Fungi (Dermatophytes). S. Peck and W. L. Hewitt. Public Health Rep., 60: 148, February, 1945.

Several members of the group of fungi occurring in clinical lesions of dermatophytosis were found to elaborate a factor antagonistic to certain other micro-organisms. This factor appeared to be similar to penicillin in the following respects: a) enhanced production on media containing corn-steep liquor, b) spectrum of activity and behavior toward penicillin-resisant organisms, c) sensitivity to pH and temperature, and d) destruction by clarase. This penicillin-like substance also was found to be produced in glucose-peptone broth by the following organisms: —T. mentagrophytes (squirrel), T. mentagrophytes (monkey), T. mentagrophytes (human), T. mentagrophytes $F_{40}R_{11}$ ultraviolet mutant, T. mentagrophytes ultraviolet mutant 107.8, T. mentagrophytes ultraviolet mutant 57.1, T. mentatrophytes ultraviolet mutant $F_{19}R_{28}$, T. mentagrophytes ultraviolet mutant 17 E 19, T. violaceum (scalp, human), T. rubrum (foot, human), T. tonsurans (human), M. canis (scalp, human), M. audouini (scalp, human), E. floccosum (foot, human).

Thrombophlebitis of the Lateral Sinus. H. Rosenwasser. Arch. Otolaryng., 41: 117, February, 1945.

The results of an analysis of 100 cases of thrombophlebitis of the lateral sinus in which the sinus was operated on at the Mount Sinai Hospital, New York, are summarized as follows: 1. The ages of 55 patients ranged up to 10 years; the ages of 90 were under 30 years. 2. An obturating thrombus was present in the lateral sinus in 12 of the 27 patients who died; 15 patients had "suppurative thrombophlebitis" or "mural thrombus" or "phlebitis." In this analysis, it was not possible to correlate the pathologic material prognostically with the clinical course. 3. Positive blood cultures were obtained preoperatively in 80 of the 97 cases in which blood was taken. In 36 of these 80 cases one or more positive blood cultures were obtained postoperatively. They were obtained from one to twenty-four days after operation, and twenty-five of them were obtained within the first seven postoperative days. The greatest expression of the pathologic process was in or about the bulb of the internal jugular vein, and in 9 cases there actually was pus within the bulb. Negative blood cultures were obtained preoperatively in 17 cases, and in 8 of these positive cultures were obtained from one to forty-two days postoperatively. In 6 of these 8, however, the positive cultures were obtained within the first eight days after operation. 4. Sixty-three patients had one or more chills preoperatively. (It is interesting to note that 37 of these were patients 10 years of age or younger.) Thirty-two patients had one or more chills postoperatively. 5. The time at which a metastatic focus becomes clinically evident is no reliable indication as to when the bacteria were deposited. In this study, metastases were noted preoperatively in 21 patients, whereas metastases were observed postoperatively in 22 patients. Of the latter, 9 also had clinical metastases before the operation on the sinus and jugular vein. 6. Changes in the ocular fundi were observed before operation in 24 patients, whereas they were noted postoperatively in 38 patients. Evaluation of the material indicated that it was not possible to correlate consistently the appearance of the fundi and the general condition of the patient at any given time. Occasionally, the changes in the fundi progressed even after the patient was well enough to be out of bed, whereas in other instances definite improvement in the fundi was noted despite the fact that the patient was still gravely ill. 7. There were 27 deaths in this group of 100 unselected patients operated on for thrombophlebitis of the lateral sinus. All operated on were included despite the presence of abscess of the brain and meningitis on admission in a number of them. The mortality from the thrombophlebitis was much higher in older patients (over 30 years) than in children and young adults. Only by including all cases can the inherent mortality of thrombophlebitis of the lateral sinus ultimately be determined. 8. Nineteen patients were treated by operation combined with chemotherapy; 17 recovered and 2 died. The influence of chemotherapy in the treatment of bacteremia is great, and because of this one must beware of the tendency on the part of some to await the effect of chemotherapy alone in cases in which the lateral sinus is involved. Therefore, until substantial evidence to the contrary is advanced, one is justified in assuming that bacteremia due to thrombophlebitis of the lateral sinus will or may persist despite chemotherapy and that surgical measures for the eradication of the phlebitic process are warranted. 9. The treatment generally employed in this series of cases consists of obliteration of the lateral sinus and ligation of the internal jugular vein. I have purposely avoided repeating the well known and oft discussed reasons for and against ligation of the jugular vein. In the last analysis I feel that the significant fundamental in the treatment is not so much the mastery of the operative procedure or the omission of part of it as it is an appreciation of the pathologic nature of the suppurative focus.

Solitary Neurofibroma of the Oral Cavity (Neurilemmona; Neurinoma). J. Schroff. J. Am. Dent. A., 32: 199, February, 1945.

Solitary benign tumors arising from the peripheral nervous system have been observed frequently in different parts of the body. They occur most frequently along the posterior division of the spinal and acoustic nerves, and less frequently along the other cranial nerves.

A review of cases at the Medical Center from 1926 to 1944 revealed only two cases involving the oral cavity and pharynx. Two additional cases are here reported. Of two rare cases of solitary neurofibroma observed in oral surgery practice, the first was that of a solid tumor found beneath the mucous membrane of the mouth and situated above the submaxillary gland. In the second case, the lesion, which was cystic, was within the ramus of the mandible. Roentgenographically, it resembled the ordinary large cyst or adamantinoma in the mandible.

Psychiatry and Propaganda. W. G. Eliasberg. J. Nerv. & Ment. Dis., 101: 225, March, 1945.

The common denominator between psychiatry and propaganda is that both deal with social relationships. A basic error of democracy, which allowed itself to be deprived of a great idealistic weapon, consists in mistaking for propaganda in general the propaganda psychology preferred by the fascists. The intellectuals, presumptive leaders of democracy, have been guilty of accepting as eternal truth certain sub-urbia beliefs on segregation between the races, religious, social rankings. As an example the so-called Differenz-affect has been analyzed. Another typical intellectual's error is the psyciatrist's habit of diagnosing certain nations with whom we happen to be at war or certain foreign nationals who never have set foot in the psychiatrist's office. Diagnostic labels vary between mania, hysteria, paranoia, etc. The crucial problem for democracy and propaganda for democracy consists in selecting that proportion of tangible and abstract contacts which are suitable at the present time. At present a great task for cooperation among psychiatrists, psychologists, sociologists, and politicans, consists in determining the role of the subleaders and of the propagandist in democracy, and working out the psychology of those specialists.

Solitary Eosinophilic Granuloma of Bone. B. B. Greenberg and A. J. Schein. Am. J. Surg., 67: 547, March, 1945.

The authors describe 2 cases of solitary eosinophilic granuloma of the long bones. It is their feeling that this condition is a well defined clinical and pathologic entity to be distinguished from similar lesions which may resemble variants of xanthomatosis or non-lipoid reticulo-endotheliosis. They emphasize the importance of biopsy and careful pathological study in order to establish the diagnosis. Treatment for this lesion consists of surgery and or radiotherapy in small doses as for inflammatory lesions. Surgery may be curettage or resection where practical without loss of function. The condition is benign. It is emphasized that solitary eosinophilic granuloma may turn out to be one of the more common of the destructive bone lesions in children and young adults and should be borne in mind in such cases.

Hardening in Industrial Allergic Dermatitis. S. Peck, J. Q. Gant, Jr. and L. Schwartz. Indust. Med., 14: 214, March, 1945.

There is ample clinical and experimental evidence to support the fact that "hardening" occurs frequently in industry. "Hardening" does not occur in all individuals. Exposure to a greater concentration of the sensitizing chemical than that to which tolerance has been established may cause a recurrence of the dermatitis until a further decrease in sensitivity occurs. "Hardening" may be permanent but in most instances it disappears if the exposure to the sensitizing chemical is discontinued for any length of time.

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